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## EXPERIMENTAL CHRONIC NEPHRITIS PRODUCED BY RADIUM

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The possibility of approaching the problems of chronic nephritis in man by reproducing the disease experimentally in animals has for years occupied the attention of many investigators. Various methods for the destruction of renal tissue have been used, including the injection of chemical substances, bacteria and bacterial toxins, partial nephrectomy, infarction of the glomeruli and roentgen irradiation. Of these methods, partial nephrectomy,<sup>1</sup> infarction of the glomeruli<sup>2</sup> and roentgen irradiation<sup>3</sup> have been reasonably successful in producing chronic renal insufficiency. None, however, has produced a lesion or a clinical condition exactly comparable to that found in man. It occurred to us that radium, because of its action on blood vessels, might be more successful in producing the desired lesions.

From the literature we were aware that the kidney is affected by radium. Horowitz<sup>4</sup> in 1911 inserted 20 mg. of radium bromide in the kidney of a rabbit for ten days and found localized areas of necrosis. Bagg<sup>5</sup> in 1920 injected large doses of an active deposit of radium emanation into white rats and dogs and reported "granular degeneration and erosion of the kidney cells." Bagg and Theis<sup>6</sup> in 1920 noted increased excretion of urinary nitrogen, especially marked on the second

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1. Chanutin, A., and Ferris, E. B.: Arch. Int. Med. **49**:767, 1932.
2. Miller, E. M., and Appelbach, C. W.: Arch. Path. **4**:193, 1927.
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4. Horowitz, cited by London, E. S.: Das Radium, Leipzig, J. A. Barth, 1911.
5. Bagg, H. J.: J. Cancer Research **5**:1 and 301, 1920.
6. Bagg, H. J., and Theis, R. C.: J. Biol. Chem. **41**:525, 1920.

day, following a large intravenous injection of radium, but they did not observe the animals over a long period of time and did not investigate the function of any of the organs affected.

The purpose of our experiments was to study the effects of intravenous injections of the active deposit of radium in dogs, with particular reference to the possibility of producing a chronic renal lesion and a generalized vascular disease. Preliminary observations disclosed that our dogs died from renal insufficiency and at postmortem examination showed small, contracted kidneys. For purposes of description, the pathologic processes and the functional changes resulting from the administration of radium may be divided into four parts:

- I. The development of the pathologic process.
- II. The effect of a single dose of the active deposit of radium injected into one renal artery.
- III. The terminal stage.
- IV. The elimination of the active deposit of radium.

#### APPARATUS AND METHODS

Radium may be administered in the form of radium salts, radium emanation or active deposit. We selected the active deposit because small tubes of radium emanation were available and we were permitted to use the specially constructed chamber devised by Blumgart and Weiss.<sup>7</sup> The active deposit of radium emanation was collected on a platinum needle electrode. The needle was removed and moistened with 10 per cent hydrochloric acid. This solution was then neutralized by the addition of 30 per cent sodium hydroxide, phenol red being used as the indicator. This solution was drawn up into a 1 cc. tuberculin syringe and the amount of radium estimated by the rate of deflection produced on the previously charged gold leaf of an electroscope. This solution was then injected, in varying dosage, into the vein of a dog within from ten to fifteen minutes. Most of the alpha rays and approximately half of the beta rays had undoubtedly disappeared within this time.<sup>8</sup> Approximately 15 per cent of the gamma ray radioactivity was also lost during this interval.

Only young, healthy dogs with normal urine, normal renal function and normal blood pressure, as shown by preliminary studies, were used. The diet (except when otherwise stated in the protocols) consisted of 1½ pounds (680 Gm.) of boiled meat per day. The following obser-

7. Blumgart, H. L., and Weiss, S.: *J. Clin. Investigation* 4:15, 1927.

8. Rutherford, E.: *Radioactive Substances and Their Radiations*, London, Cambridge University Press, 1913, p. 487. Simpson, F. E.: *Radium Therapy*, St. Louis, C. V. Mosby Company, 1922, pp. 26 and 320. Colwell, H. A., and Russ, S.: *Radium, X-Rays and the Living Cell*, New York, Harcourt, Brace and Company, 1924, p. 79.

vations were made at regular intervals: weight in kilograms; rectal temperature; routine urinalysis on fresh specimens; blood pressure by the auscultatory method on the foreleg, a standard mercury sphygmomanometer being used; red blood count, white blood count and hemoglobin content by the Sahli method; amounts of urea nitrogen, nonprotein nitrogen and creatinine<sup>9</sup> per hundred cubic centimeters of blood; amounts of cholesterol,<sup>10</sup> chloride<sup>11</sup> and total protein<sup>12</sup> per hundred cubic centimeters of blood. All examinations of the blood were made on venous blood withdrawn while the animal was fasting.

Eighteen dogs, including one control, were used. The control was given intravenous injections of the neutralized acid-base mixture to which no radium was added. Complete gross and microscopic studies were carried out on all animals, including the control. In the latter, the findings were absolutely normal throughout.

#### I. THE DEVELOPMENT OF THE PATHOLOGIC PROCESS

The observations in five dogs (series A) illustrates the development of the pathologic process in the kidneys.

*Procedure.*—Dogs 1, 2 and 3 received intravenous injections in doses varying from 11 to 15 millicuries of the active deposit of radium twice a week throughout the experiments, in order to minimize as much as possible reparative processes. In dogs 4 and 5, the injections of radium were discontinued after the seventeenth and forty-fourth days, respectively. The following observations were recorded twice a week: blood pressure, body weight, temperature, complete urinalysis, red blood count, white blood count and hemoglobin content. The blood chemistry, including the blood urea nitrogen, nonprotein nitrogen, cholesterol, chloride, creatinine and total protein, was determined once a week. The animals were killed at eight, thirty, fifty, seventy-three and eighty-two days, respectively. A complete autopsy was performed on each immediately, and the tissues were fixed in Zenker's solution and stained with hematoxylin-eosin and phosphotungstic acid. Frozen sections of formaldehyde-fixed renal tissue were stained with scarlet red for fat.

*Protocols.*—Dog 1.—This was a shepherd dog, weighing 16.6 Kg. A total of 30 millicuries of the active deposit of radium was given in two injections. The dog remained in good health throughout the experiment and gained 0.5 Kg. in weight. The leukocyte count dropped from 10,000 to 7,500 per cubic millimeter. The temperature remained within normal limits. The blood pressure, urinalysis, red blood count and blood chemistry remained within normal range. The dog was killed on the eighth day. No significant changes were found in any of the organs by gross or histologic examination. The right and left kidneys weighed 55.5 and 50.5 Gm.

9. Folin, O.: *Laboratory Manual of Biological Chemistry*, ed. 4, New York, D. Appleton & Company, 1925.

10. Bloor, W. R.; Pelkan, K. F., and Allen, D. M.: *J. Biol. Chem.* **52**:191, 1922.

11. Whitehorn, J. C.: *J. Biol. Chem.* **45**:449, 1921.

12. Hawk, P. B., and Bergheim, O.: *Practical Physiological Chemistry*, ed. 9, Philadelphia, P. Blakiston's Son & Co., 1926.

DOG 2.—This was a shepherd dog, weighing 22 Kg. A total of 110 millicuries of radium was given in eight injections at the rate of two injections a week. There was a gradual reduction in the leukocytes from 8,500 to 3,600, while the erythrocytes increased from 6,300,000 to 7,500,000. The temperature, blood pressure and body weight remained constant. There was no alteration in the urinalysis or in the blood chemistry. The dog remained in good health throughout the experiment and was killed on the thirtieth day. At autopsy, the abdominal organs appeared moderately congested, but no other gross abnormality could be detected. The kidneys weighed 59 and 62 Gm. Each was normal in size and shape and appeared pale reddish gray. The capsules stripped with ease, exposing a smooth, glistening surface with a few scattered small depressions. On the cut surface, the markings were well preserved, and the differentiation was good. The cortex measured from 9 to 11 mm. and the medulla from 15 to 18 mm. There was no increase in the pelvic fat. Histologic examination revealed normal conditions in all organs except the kidneys.

Sections of the kidneys showed definite glomerular and tubular changes. The glomeruli showed hyaline thickening of the tuft arterioles, but these contained a normal amount of blood. There was no proliferation of the cells lining the glomerular capsules. The convoluted and collecting tubules were the seat of marked diffuse, though patchy, degeneration. Henle's loops appeared comparatively normal. No swelling or fragmentation of collagen fibers or proliferation of the connective tissue could be seen. The larger blood vessels were normal.

DOG 3.—This was a shepherd dog, weighing 21.4 Kg. A total of 155 millicuries of radium was given in thirteen injections, two each week. The leukocytes rose from 14,700 to 16,200 after the first injection, but fell to 7,600 after the second injection, then gradually decreased to 4,700 after the eighth injection on the twenty-ninth day. They rose again to 5,800 on the fiftieth day. The erythrocytes increased from 6,760,000 to 7,200,000, and the hemoglobin increased from 11 to 11.5 Gm. per hundred cubic centimeters of blood. The blood pressure fluctuated over a wide range, but tended to be slightly elevated. The temperature, urinalysis and blood chemistry remained within normal limits. The dog maintained good health, gaining 2.6 Kg. during the experiment. She was killed on the fiftieth day. At autopsy, no gross pathologic changes were seen in any of the organs with the possible exception of the kidneys. These appeared large, weighing 84 Gm. each. The capsule stripped with slightly increased difficulty, exposing a mottled, reddish-brown surface with numerous scattered small depressions and irregularly distributed white dots from 1 to 1.5 mm. in diameter. The cut-surface was pale reddish brown, with good differentiation and normal-appearing cortical striations. The cortex measured from 9 to 11 mm. and the medulla from 15 to 17 mm. Histologic sections of the kidneys showed hyaline changes in the glomerular arterioles and in some arterioles outside the glomeruli. Most of the glomeruli appeared quite vascular and some showed slight thickening of the capsules (fig. 1). There was definite tubular damage with fragmentation of the cells. Some of the cells of the tubules showed mitotic figures. The hyaline membrane at the base of the tubular epithelium frequently appeared thickened. There was also a definite patchy increase in the interstitial tissue between damaged tubules.

DOG 4.—This was an Airedale, weighing 15.3 Kg. A total of 148 millicuries of radium was given in eight injections during the first seventeen days. The leukocytes diminished from 6,200 to 2,000 by the twenty-first day, but gradually returned to normal by the thirty-sixth day. The dog remained in good health and gained weight up to the fiftieth day. Shortly after this it was noted that he ate poorly and was beginning to lose weight. The first sign of renal impairment

appeared on the fifty-seventh day in elevated blood urea nitrogen—37 mg. per hundred cubic centimeters of blood and nonprotein nitrogen—50 mg. per hundred cubic centimeters of blood. Two weeks later, on the seventy-first day, urinalysis showed a drop in specific gravity from 1.052 to 1.016, with a slight trace of

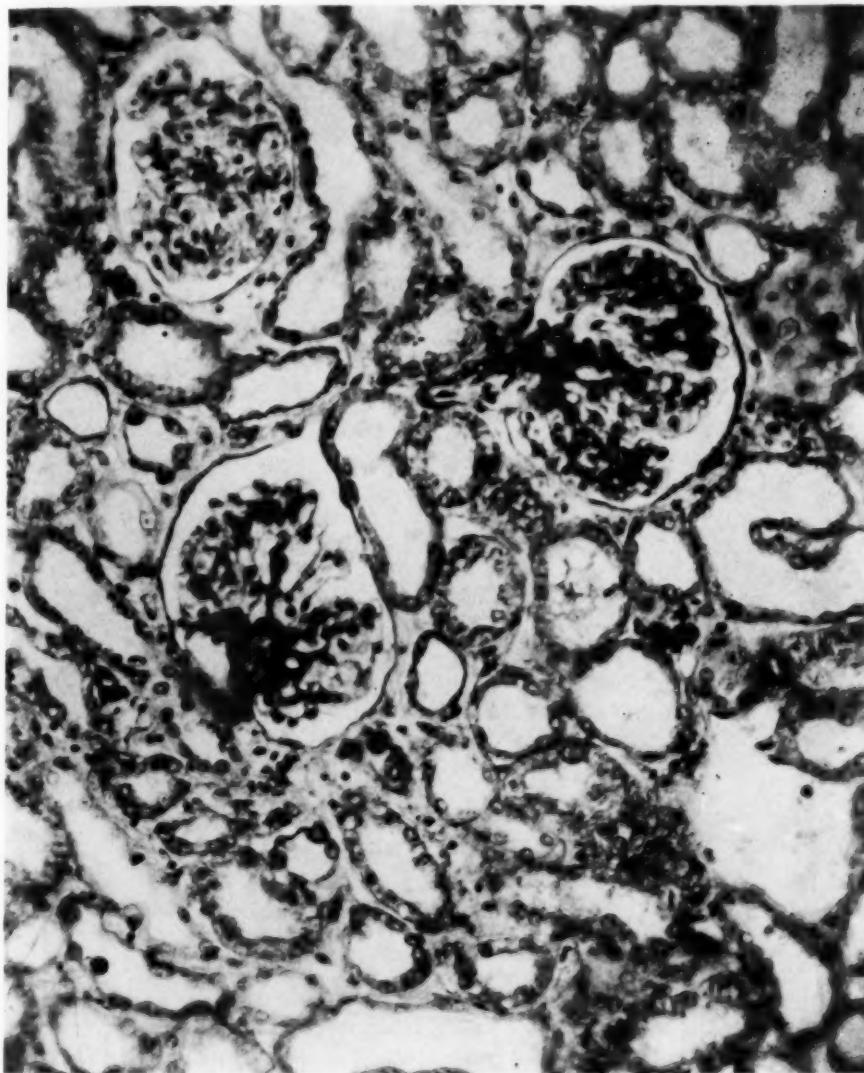


Fig. 1 (dog 3).—Early glomerular and tubular changes resulting from intravenous injections of radium over a period of fifty days. Hyalinization of the glomeruli is indicated by the darker areas. The vascularity is not greatly reduced. Note the vacuolization and degeneration of the tubular epithelium;  $\times 250$ .

albumin and a rare granular cast. The blood pressure varied, but tended to be lower than the control observations. The temperature remained normal. After

the fifty-seventh day, the blood urea nitrogen and nonprotein nitrogen rose to 56 and 83 mg., respectively. The dog lost weight rapidly, refused food and was killed on the seventy-third day, sixteen days after the onset of the signs of renal insufficiency. The kidneys were the only organs to show gross pathologic changes.

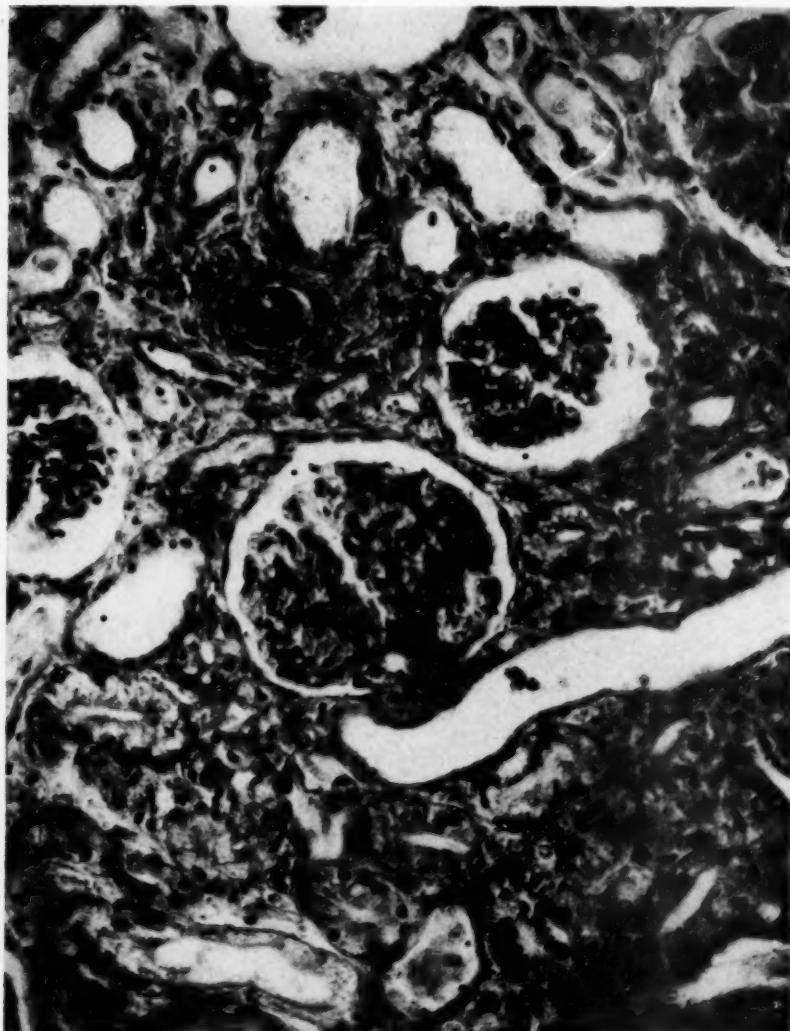


Fig. 2 (dog 2).—Intermediary stage of effects of radium injected intravenously over a period of seventy-three days. Contrast with figure 1. Note the increased hyalinization of the glomeruli, the increased destruction of tubules, and particularly the well marked sclerosis in the vessels in the upper part of the field;  $\times 250$ .

Each kidney weighed 42 Gm. They were small and reddish brown. The capsules stripped with slightly increased difficulty, exposing a finely irregular, glistening surface. The cut surface was pale reddish brown, with good differentiation of the

cortex and medulla and slightly indistinct cortical striations. The arcuate arteries appeared prominent. The cortex measured from 5 to 7 mm., and the medulla, from 12 to 15 mm. The kidneys were the only organs in which pathologic changes were found microscopically. The sections showed marked hyalinization and thickening of the glomerular arterioles. Most of the glomeruli appeared pale and bloodless with definite thickening of the capsules. There were diffuse degenerative changes in the tubular epithelium, and many of the cells showed mitotic figures. A relatively slight patchy increase in the fibrous connective tissue was visible (fig. 2).

Dog 5.—This was a pointer, weighing 16 Kg. Radium was given daily for the first four days, again on the twenty-first and twenty-second days, then daily from the twenty-sixth to the thirtieth day, and finally on the forty-third and forty-fourth days. The total dosage was 170 millicuries. The experiment lasted eighty-two days. The leukocyte count gradually diminished from 10,600 to 3,000 by the ninth day, but returned to 10,100 by the twenty-first day. When the injections were resumed on the twenty-sixth day, the white cells gradually diminished to 3,000 by the fortieth day, returning to normal by the sixty-fifth day and remained approximately 11,000 till the end. The erythrocytes increased slightly from 6,800,000 to 7,150,000. The blood pressure fluctuated within the normal range during the first seven weeks, but after the fiftieth day fell below normal. The temperature remained normal. The dog remained in good health and gained weight up to the fifty-first day, after which he rapidly lost weight and became weak and drowsy. Signs of renal insufficiency were first detected on the sixty-second day in a rise of blood urea nitrogen to 42 mg. and in nonprotein nitrogen to 73 mg. per hundred cubic centimeters. Three days later, on the sixty-fifth day, the urinalysis showed the specific gravity lowered from 1.045 to 1.010, with a very slight trace of albumin. Subsequent urinalyses showed a persistent low specific gravity, increasing albumin and rare to moderate hyaline and granular casts. The blood urea nitrogen and nonprotein nitrogen rose to 112 and 174 mg. on the seventy-ninth day. The dog was killed on the eighty-second day, twenty days after the onset of signs of renal insufficiency. Gross and histologic examination revealed no abnormality apart from the kidneys. The kidneys weighed 39 and 40 Gm. They were small, but of normal shape and color. The capsule stripped with increased difficulty, exposing a smooth, grayish-pink surface with numerous scattered grayish-white dots. On the cut surface, the differentiation was well marked. The arcuate arteries appeared prominent. The cortex measured from 6 to 8 mm., and the medulla from 12 to 15 mm. The sections of the kidney showed a bloodless condition of the glomerular tuft with marked hyaline changes in the arterioles inside and outside the glomeruli and thickening of the glomerular capsules. The convoluted tubules were the seat of marked degeneration. There was a most striking diffuse increase in the interstitial connective tissue to a degree approaching the end-stage seen in the kidneys of series C.

Table 1 summarizes the clinical findings in series A. The dogs were of fairly uniform size and weight. The total radium dosage was graded from 30 to 170 millicuries. The duration of the experiments varied from eight to eighty-two days. Dogs 1, 2 and 3 were killed while still in apparently good health, whereas dogs 4 and 5 were killed from sixteen to twenty days after the signs of renal insufficiency had appeared. Dog 4 was beginning to lose weight rapidly, while dog 5 was already somewhat emaciated. The last column (table 1) shows a relatively marked reduction in the weights of the kidneys of dogs 4 and 5.

In series A, the first clinical evidence of a serious effect of the radium was a loss of appetite and of weight which began about the fiftieth day after the first injection of radium. From that time on there were progressive weakness, apathy and loss of weight, but no other toxic symptoms. The first sign of renal damage appeared in the form of a retention of nitrogen in the blood, starting about ten days after the animal first appeared sick and progressing steadily to death. The proteins of the blood were unaffected. Curiously enough there were no urinary abnormalities for several days after the elevation of the blood urea nitrogen. Then appeared a marked often abrupt lowering of the specific gravity, with albuminuria and cylindruria. No well defined hypertension was observed in any animal.

The earliest demonstrable lesion was detected at the end of thirty days; it consisted of a hyaline change in the arterioles of the glomerular tuft and degeneration of the cells of the convoluted tubules. At the end

TABLE 1.—*Results of Intravenous Injection of Radium in Series A*

Dog	Original Weight, Kg.	Radium Dosage, Mc. per Kg.	Total Mc.	Duration of Administration, Days	Days to Renal Insufficiency	Days from Renal Insufficiency to Death	Average Weight of Kidneys, Gm.
1	16.6	2	30	8	..	..	53.0
2	22.0	5	110	30	..	..	60.0
3	21.4	7	155	50	..	..	84.0
4	15.3	10	148	73	57	16	41.0
5	16.0	11	170	82	62	20	39.5

Mc. = millieuries.

of fifty days, these changes became more pronounced, and, in addition, there were swelling of the basement membranes of the tubular epithelium, visible patchy increase in connective tissue and sclerosis of some of the arterioles outside the glomeruli. At the end of seventy-three and eighty-two days, arteriolar sclerosis was well defined. There was a conspicuous relative increase in connective tissue with resulting contraction of the kidneys.

Wolbach<sup>13</sup> in 1924 reported that the earliest demonstrable histologic change in the skin of animals exposed experimentally to roentgen rays was a striking swelling of the collagen of the corium and subcutaneous tissue, with later necrosis and substitution by proliferation of fibroblasts and the laying down of new collagen fibers. This reaction took place not only in the corium of the skin, but also in the walls of blood vessels, accounting for the thickening and eventually for the occlusion of the blood vessels. The changes in the epithelium became manifest only after the collagen changes had become evident.

13. Wolbach, S. B.: Am. J. Roentgenol. 13:139, 1925.

The histologic changes, namely, the hyalinization of the glomeruli, the swelling of the basement membranes, and the diffuse fibrosis in the kidneys of our dogs, are, in our opinion, similar in nature to those reported in the skin. The changes are interpreted as indicating a general effect of the radium on the cement and collagen substances in the glomerular tufts, the arterioles and the interstitial tissues, including the basement membranes. The presence of mitotic figures in the atrophic tubules shows that the reparative properties had not been completely destroyed and hence is against the principal effect of the radium being on the tubular epithelium. No doubt the hyalinization of the basement membrane played a more important rôle in the destruction of the tubules than the radium itself.

## II. EFFECT OF INJECTION OF A SINGLE DOSE OF RADIUM INTO ONE RENAL ARTERY

In order to study further the direct effect of radium on the kidney, the active deposit was injected into one renal artery. Two dogs (series B) were used.

*Procedure.*—Under aseptic surgical technic the kidneys were exposed extraperitoneally through a transverse incision in the flank. The solution was diluted in 5 cc. of sterile saline solution and injected slowly into the renal artery. The wounds were closed without drainage and healed promptly.

*Protocols.*—Dog 6.—This was a collie, weighing 15.9 Kg. Thirty millicuries of radium was injected into the left renal artery within fifteen minutes of preparing the radioactive solution. The experiment lasted fifty-eight days. The leukocytes decreased from 14,500 to 9,000 per cubic millimeter. The blood pressure rose slightly during the first thirty days, but returned to normal on the fifty-sixth day. The erythrocytes decreased from 6,060,000 to 5,600,000. The weight increased 0.6 Kg. during the first thirty days, but returned to the control level by the fifty-eighth day. The temperature remained normal.

Signs of renal insufficiency appeared first on the forty-second day as an elevation of the blood urea nitrogen and nonprotein nitrogen to 42 and 70 mg. per hundred cubic centimeters, respectively. One week later, on the forty-ninth day, urinalysis showed the specific gravity decreased from 1.030 to 1.010, with a very slight trace of albumin. Subsequent urinalyses showed a persistent low specific gravity and a slight trace of albumin. No casts or red blood cells were found. The blood urea nitrogen and nonprotein nitrogen steadily rose to 114 and 150 mg. on the fifty-sixth day. The dog showed increasing irritability.

On the fifty-eighth day, 500 cc. of saline solution was given by stomach tube, and under diallyl-barbituric acid anesthesia specimens of urine were obtained by ureteral catheterization for the purpose of estimating the relative function of each kidney. At the end of an hour, 410 cc. of urine was obtained from the right side, and only 10.5 cc. from the left side. Both specimens showed a slight trace of albumin, but no casts or red blood cells were found. The animal was then killed.

At autopsy, the left kidney appeared to be only half the size of the right (fig. 3). The right kidney weighed 46.3 Gm., and appeared to be normal in size and shape. The capsule stripped with slightly increased difficulty, exposing a reddish-brown,

slightly irregular surface with a few scattered white dots. The cut surface was pale brown with good differentiation. The cortex measured from 6 to 8 mm., and the medulla, from 14 to 16 mm.



Fig. 3 (dog 6).—The kidneys fifty-eight days after a single injection of 30 millicuries of radium into the left renal artery. Note the uniformly shrunken left kidney weighing 22 Gm. The right kidney weighed 46 Gm.

The left kidney, weighing 22.3 Gm., appeared uniformly shrunken, but normal in shape and color. The capsule showed a few adhesions to tissues surrounding

the posterior part. The capsule stripped with markedly increased difficulty, exposing a reddish-brown, coarsely irregular, wrinkled surface, with a few scattered white dots. On the cut surface the differentiation was good. The cortex, measuring from 3 to 4 mm., was brownish yellow with exaggerated linear striations. The arcuate arteries stood out prominently. The medulla measured from 9 to 10 mm.

Sections from the right kidney showed a diffuse, though scattered, increase in the fibrous connective tissue stroma replacing the normal renal structures, but leaving isolated groups of convoluted tubules showing marked degeneration and

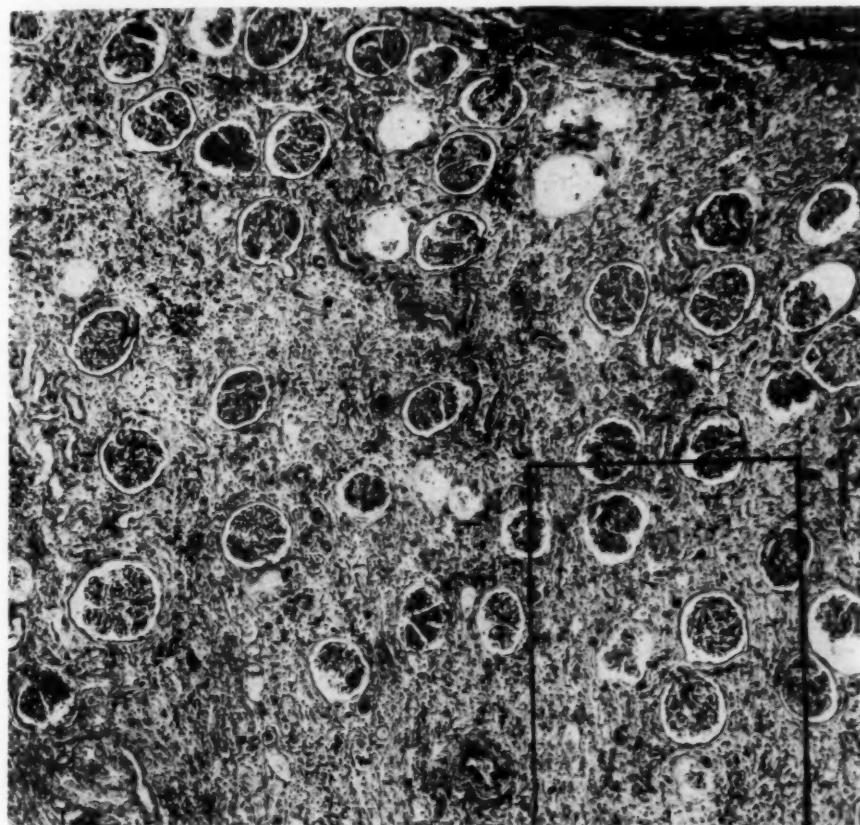


Fig. 4 (dog 6).—Low power magnification of the left kidney seen in figure 3. Note the marked increase in fibrous tissue and the tubular destruction;  $\times 80$ .

vacuolization. The glomeruli disclosed hyalinization of the tuft arterioles and slight thickening of the capsules. No abnormality of the arteries could be seen. There were, in addition, scattered focal necrotic lesions, consisting of localized areas of lymphocytic and polymorphonuclear infiltration with central necrotic areas.

Sections from the left kidney (figs. 4 and 5) showed a marked, uniform, diffuse fibrous tissue increase and lymphocytic cellular infiltration throughout the stroma with scattered localized follicle formation. The few remaining convoluted tubules showed marked degenerative changes with fat-laden cells. The glomeruli appeared relatively abundant, separated only by bands of fibrous tissue. They appeared

bloodless with varying degrees of hyalinization and degeneration of the tufts. Bowman's capsules everywhere showed marked proliferative changes with thickening. The smaller blood vessels showed thickening and hyalinization of their walls, while the larger blood vessels appeared intact.

DOG 7.—This terrier, weighing 11.8 Kg., was given one injection of 10 milli-curies into the right renal artery. The dog was killed one hundred and twelve days

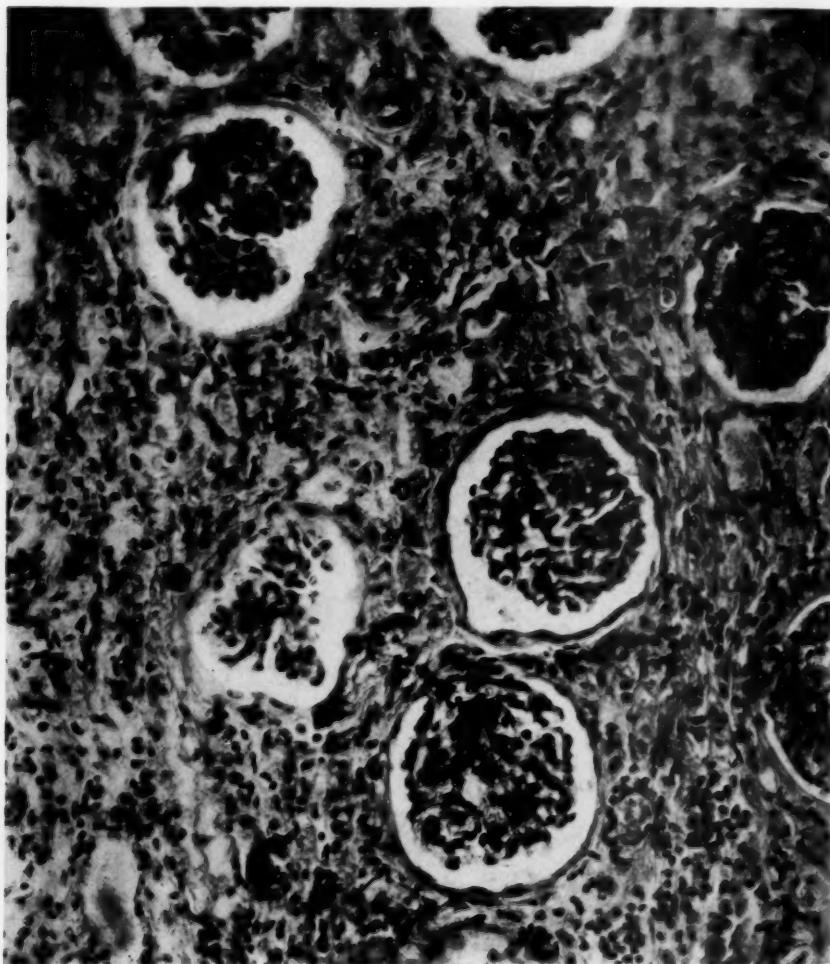


Fig. 5 (dog 6).—Higher magnification of the rectangular area marked out in figure 4. Note the absence of tubules, the fibrosis accompanied by lymphoid infiltration, the hyalinization and sclerosis of arterioles, the thickened capsules and the avascularity of the glomeruli;  $\times 250$ .

later, having shown no clinical evidence of a radium effect. At autopsy, the only gross finding was a scar in the upper pole of the right kidney. Dissection and microscopic sections showed only the presence of an infarct due to a localized thrombosis.

A single relatively small dose of the active deposit of radium injected directly into one renal artery produced marked renal insufficiency and marked shrinkage of the involved kidney in one of the two dogs. The weight of the affected kidney was less than half that of the unaffected one. The reduction of renal tissue was uniform, involving both the cortex and the medulla. Histologically, the kidney receiving the radium showed extreme glomerular, tubular, interstitial and vascular changes similar in type to the end-stage seen in figure 6. The opposite kidney showed similar but less marked changes, comparable to those seen in figure 1, the fifty day experiment. The focal lesions found in both kidneys were not found in any of the other dogs and are not regarded as due to the radium. Ureteral catheterization immediately before death showed a definitely smaller urinary output from the affected kidney. This would indicate that radium injected directly into one renal artery initiated a relatively greater destructive process owing to increased concentration.

The failure to obtain any evidence of diffuse damage in the kidney of the other dog may be due to the extremely small dose. The gross scar found at autopsy was the result of a localized thrombosis, probably caused by the operative procedure.

### III. THE TERMINAL STAGE

Functional and pathologic studies were made on six dogs (series C) dying from the effects of intravenous injections of small doses of the active deposit of radium. Five were allowed to die from the effects of the radium and one was killed while moribund. The active deposit of radium was injected intravenously at irregular intervals and in varying amounts, because of the difficulty of obtaining at the time a uniform supply. However, enough was injected to maintain a relative leukopenia. Table 2 (dog 8) illustrates the findings in series C.

*Protocols.*—DOG 8.—This was a shepherd dog, weighing 18.5 Kg. Following the preliminary control studies, the active deposit of radium was injected daily for the first four days, once on the twenty-first day, daily from the twenty-sixth to the twenty-ninth day, then daily from the forty-third to the forty-fifth days, and finally on the seventy-seventh day—making a total dosage of 169 millicuries. The experiment lasted one hundred and twelve days. The first noticeable effect was a fall in the leukocyte count from 6,600 to 3,200 per cubic millimeter on the fourth day following the first injection. This fall persisted until the sixteenth day and then returned to normal. After the injections on the twenty-sixth, twenty-seventh, twenty-eighth and twenty-ninth days, there was a second fall to 4,000, but within eight days the count had returned to normal. When the injections of radium were resumed on the forty-third, forty-fourth and forty-fifth days, the leukocyte count again decreased and did not return to normal until the seventy-sixth day. The dog's appetite and general appearance remained good throughout this period. The first signs of renal impairment appeared on the eighty-fourth day as indicated by a rise in blood urea nitrogen to 28 mg. and in nonprotein nitrogen to 59 mg. One

TABLE 2.—Data on Dog 8, Series C. Terminal Stage

No. of Days	Date	Blood		Blood Chemistry		Blood Pressure		Urinalysis		Sediment		Comment		
		Red Blood Cells	White Blood Cells	Differentiable	Nonprotein Nitrogen	Total Protein	Chlorides	Syphilic	Diseasome	Specific Gravity	White Blood Cells	Red Blood Cells		
1	4/2/31	16	13.0	6,200	6,000,000	Normal	13	38	240	285	1.012	0	101.2	
2	4/3/31	14	13.5	6,600	6,140,000	Normal	10	37	285	347	1.010	0	102.5	
3	4/4/31	12	12.0	6,600	6,720,000	Normal	10	37	285	347	1.010	0	102.4	
4	4/5/31	8	12.0	6,600	5,930,000	Normal	10	37	285	347	1.010	0	102.4	
5	4/6/31	0	12.0	6,600	5,000,000	Normal	8	34	280	347	1.010	0	101.1	
6	4/7/31	17.7	0	12.5	5,940	Abnormal*	10	37	285	347	1.010	0	102.5	
7	4/8/31	17.6	0	12.5	5,940	Normal	10	37	285	347	1.010	0	102.5	
8	4/9/31	17.8	0	13.0	3,800	Normal	10	37	285	347	1.010	0	102.5	
9	4/10/31	17.8	0	13.0	3,800	Normal	10	37	285	347	1.010	0	102.5	
12	4/13/31	17.7	0	13.5	4,600	6,780,000	Abnormal	7	32	260	304	1.012	0	102.6
15	4/16/31	17.6	0	13.0	6,400	6,400,000	Abnormal	10	37	285	347	1.010	0	102.3
21	4/22/31	17.4	0	12.0	6,800	5,940,000	Abnormal	18	34	280	347	1.010	0	102.2
26	4/27/31	17.7	0	11.8	7,300	Normal	10	37	285	347	1.010	0	102.2	
27	4/28/31	17.1	15	6,600	5,800	Normal	10	26	295	355	1.012	0	102.2	
28	4/29/31	17.1	12	5,800	5,800	Normal	10	26	295	355	1.012	0	102.2	
29	4/30/31	17.9	0	14.0	4,000	Normal	10	26	295	355	1.012	0	102.2	
30	5/1/31	17.8	0	13.0	6,200	7,250,000	Normal	10	26	295	355	1.012	0	102.2
41	5/11/31	17.6	0	14.0	7,800	7,500,000	Normal	15	40	280	355	1.012	0	101.6
43	5/18/31	16	16	7,700	7,700	Normal	21	42	294	356	1.010	0	102.4	
44	5/14/31	17.1	12	4,100	4,100	Normal	10	26	295	355	1.012	0	102.4	
45	5/15/31	17.1	12	4,100	4,100	Normal	10	26	295	355	1.012	0	102.4	
48	5/18/31	17.1	10	14.5	3,400	7,800,000	Normal	6	34	160	280	1.012	0	102.4
55	5/25/31	16.7	0	14.0	4,700	8,100,000	Normal	8	31	280	355	1.012	0	101.0
66	6/1/31	16.3	0	14.5	4,600	7,150,000	Normal	15	40	280	355	1.008	0	102.4
76	6/15/31	16.3	0	14.5	7,400	8,000,000	Abnormal*	18	43	280	355	1.012	0	102.4
84	6/28/31	15.2	0	14.0	7,900	8,350,000	Normal	28	50	280	355	1.012	0	102.4
91	6/30/31	15.7	0	13.0	5,200	8,200,000	Normal	45	61	215	355	1.012	0	102.4
98	7/7/31	14.4	0	14.0	5,200	8,900,000	Normal	31	61	215	355	1.012	0	102.4
100	7/10/31	13.6	0	14.0	5,200	8,900,000	Normal	33	66	215	355	1.012	0	102.4
104	7/14/31	11.5	0	15.0	7,650	8,250,000	Abnormal*	78	155	250	355	1.018	0	101.6
110	7/20/31	11.5	0	15.5	10,800	7,600,000	Normal	115	192	250	355	1.014	0	101.7
112	7/22/31	0	0	0	0	0	0	0	0	0	0	0	0	

\* Relative increase in lymphocytes.

† Postmortem examination performed within 45 minutes.

week later, on the ninety-first day, the slightest possible trace of albumin, very rare red blood cells and rare hyaline casts were detected in the urine for the first time. From this time on, the dog was lethargic, ate little and lost weight rapidly. The skin was noticeably loose and flabby, and the subcutaneous tissue disappeared, leaving bony prominences. The nose became dry and crusted, the breath foul and the eyes sunken in their sockets. The urine repeatedly showed albumin and rare granular casts. The nitrogen retention increased until the urea nitrogen reached 115 mg. and the nonprotein nitrogen 192 mg. on the day before death. The

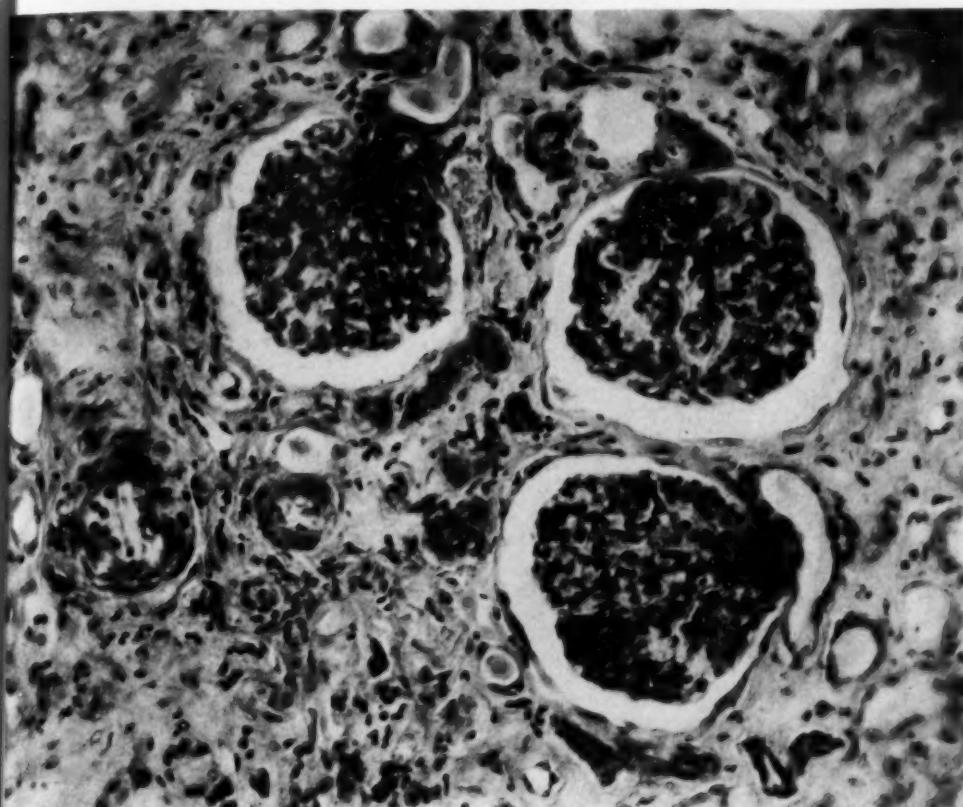


Fig. 6 (dog 9).—End-stage of the effects of intravenous injection of radium over a period of one hundred and forty-five days. Contrast with figures 1 and 2. Note the marked destruction of tubules, the marked increase in fibrous tissue, the increased thickening of the glomerular capsules, the closing of the capillaries of the tufts with decreased vascularity and increased cellularity of the tufts, and the marked arteriosclerosis, particularly in the vessels just to the right of the upper left glomerulus;  $\times 250$ .

creatinine rose to 6.7 mg. The dog lost 7 Kg. in all, 4.8 Kg. during the last thirty-six days. There was no alteration in the body temperature. The blood cholesterol, blood chlorides and serum proteins remained unchanged. The hemoglobin content and the erythrocytes of the blood definitely increased.

Postmortem examination made within forty-five minutes after death showed marked emaciation and dehydration, but no visible changes in the bones and other organs except in the abdomen and lower lobes of the lungs, which appeared some-

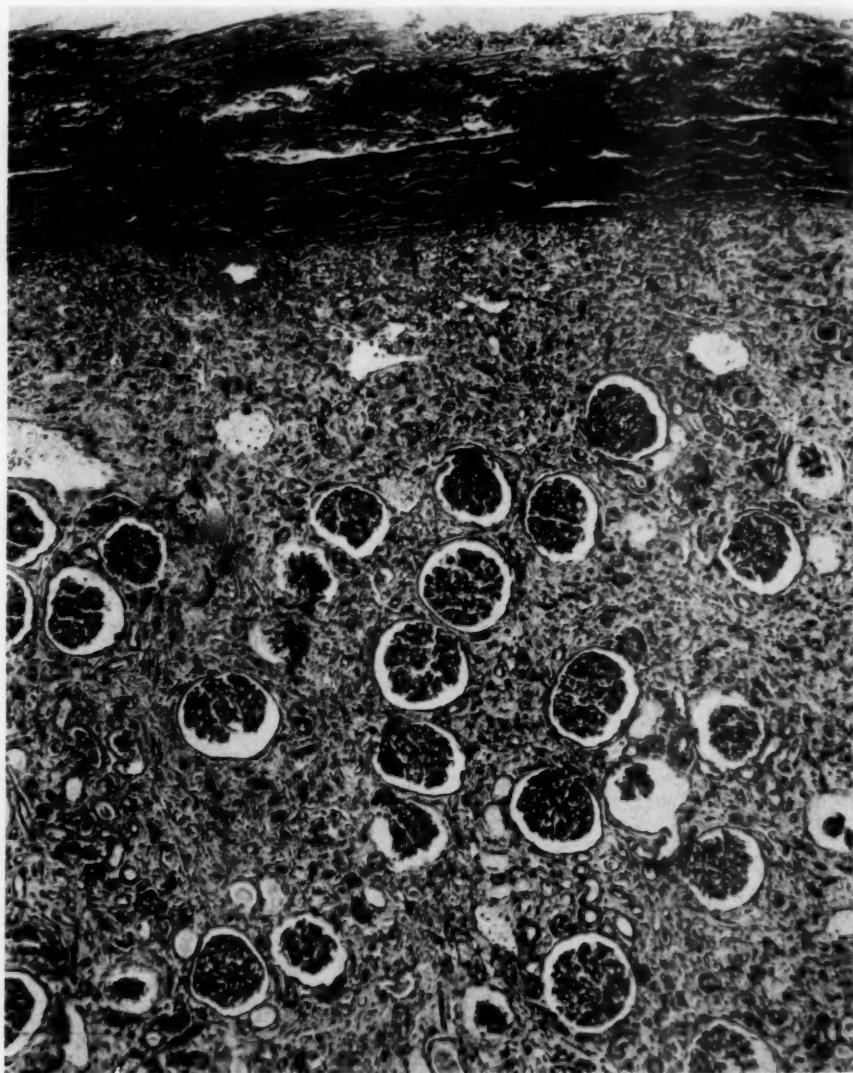


Fig. 7 (dog 9).—Low power magnification of figure 6. This illustrates more clearly the extent of tubular degeneration and the marked increase in fibrous tissue;  $\times 80$ .

what congested. The heart weighed 96 Gm. Both kidneys were small but normal in shape and color, weighing 23.3 and 24.4 Gm. The capsules stripped with slightly increased difficulty, exposing a smooth, reddish-brown surface. On the cut surface,

the differentiation was good. The cortex measured from 4 to 5 mm., and the medulla, from 10 to 12 mm. Microscopically, the lungs showed edema and congestion of the lower lobes with localized areas of extravasated red blood cells and a few polymorphonuclear leukocytes. The liver disclosed slight congestion and atrophy of the columns around the central veins. Sections of the spleen, heart, pancreas, suprarenal glands, thyroid gland, bone marrow, lymph nodes and small intestine showed no noticeable changes. The kidneys showed most strikingly a diffuse increase in the fibrous connective tissue stroma, with marked degeneration of the tubules. Sections stained with scarlet red showed increased amounts of fat in the convoluted tubules, as compared with the control. The glomeruli appeared bloodless with marked hyaline thickening of the tuft arterioles and marked thickening of the glomerular capsules. The walls of many of the smaller arteries and arterioles showed moderate to extreme thickening and sclerosis.

DOG 9.—This was a shepherd dog, weighing 14.9 Kg. The active deposit of radium was given in six small doses totaling 61 millicuries over a period of sixty-four days. The duration of the experiment was one hundred and forty-five days.

The leukocytes gradually diminished from 9,600 to 6,000 per cubic millimeter during the first forty-nine days, returning to 10,600 per cubic millimeter on the sixty-fourth day. From this time until death the leukocyte count remained at approximately 8,000 per cubic millimeter, except on two occasions when the counts were 11,000 and 5,000.

The first indication of renal insufficiency, as evidenced by elevated values for blood nitrogen, appeared on the sixty-fourth day when the urea nitrogen and non-protein nitrogen were 39 and 64 mg. per hundred cubic centimeters, respectively. The dog remained in good physical condition and gained 0.6 Kg. in weight during this time. In order to study the relationship between the protein intake and the nitrogen retention, the protein in the diet was reduced to 15 Gm. on the seventy-first day—adequate caloric intake being maintained by the addition of carbohydrate and fat. Six days later, on the seventy-seventh day, the blood urea nitrogen and the nonprotein nitrogen had dropped to 15 and 28 mg. per hundred cubic centimeters, respectively, and remained within normal limits until the one hundred and twenty-fifth day. During this interval, however, the blood creatinine rose gradually from 1.3 to 3.2 mg. per hundred cubic centimeters, and the specific gravity of the urine decreased from 1.036 to 1.010. As the dog was losing weight and becoming progressively weaker, the protein in the diet was increased to 100 Gm. daily. One week later, on the one hundred and thirty-third day, the diet was again reduced because the blood urea nitrogen was elevated to 96 mg. Despite this lowered protein intake, the blood urea nitrogen rose to 126 mg. and the nonprotein nitrogen to 228 mg. on the one hundred and fortieth day. Creatinine rose to 12.5 mg. The urine showed the slightest possible trace of albumin, for the first time, on the one hundred and nineteenth day. Subsequent urinalyses showed lowered specific gravity and increasing amounts of albumin. A very rare granular cast was found on one occasion, but this observation was not confirmed—possibly owing to the alkaline reaction of subsequent specimens of urine.

At no time was there any appreciable change in the blood pressure or in the body temperature. No edema was demonstrable. The blood cholesterol increased from 156 to 385 mg. per hundred cubic centimeters on the one hundred and twenty-fifth day and was 265 mg. on the one hundred and fortieth day, five days before death. There was no evidence of chloride retention or of serum protein depletion. The erythrocyte count remained within normal limits until the last two weeks when it dropped from 7,330,000 to 4,380,000. The dog became progressively weaker and was killed in a moribund condition by intracardiac injection of 20 cc. of ether on the one hundred and forty-fifth day.

An autopsy, made immediately, showed marked emaciation and uniformly small kidneys; otherwise nothing grossly abnormal could be seen. The kidneys were small and uniformly shrunken, and weighed 18 and 18.5 Gm. The capsule stripped with slightly increased difficulty, exposing a smooth, reddish-brown surface with scattered, slightly elevated white spots about the size of a pinhead. On the cut surface, the differentiation was fairly good. The cortex measured from 3 to 4 mm., and the medulla, from 9 to 11 mm. in width. There were no gross changes in the blood vessels and no increase in the pelvic fat of the kidneys. Microscopic examination showed a most pronounced diffuse fibrosis throughout the stroma, with scattered islands of degenerated, fat-laden tubular remnants and marked hyalinization of the glomerular arterioles and thickened glomerular capsules. None of the glomeruli appeared entirely normal (figs. 6 and 7). A section of heart muscle with a coronary artery showed infiltration by lymphocytes and polymorphonuclears in the media of the arterial wall extending into the surrounding tissue between the muscle fibers. In one area, this infiltration extended to the endocardial surface. Routine sections of the various other organs showed no changes.

DOG 10.—This was a terrier, weighing 8.6 Kg. Radium was injected on the first three days, on the ninth and again on the sixteenth day. The total dosage was 65 millicuries. The experiment lasted sixty-two days.

Within twenty-four hours after the first injection the leukocyte count decreased from 14,200 to 6,000 per cubic millimeter; the count then gradually fell to 2,200 on the twenty-second day. By the forty-third day, it reached 13,400 and remained within normal limits to the end of the experiment.

The first indication of functional disturbance of the kidneys appeared on the thirty-sixth day as a rise in blood urea nitrogen to 24 mg. per hundred cubic centimeters and in nonprotein nitrogen to 43 mg. These subsequently increased to 126 and 160 mg. on the fifty-sixth day. The creatinine remained normal until the forty-ninth day and then rose from 1.3 to 2.7 mg. by the fifty-sixth day. Before death it had risen to 9.7 mg. The blood pressure fluctuated between 100 systolic and 75 diastolic and 140 systolic and 100 diastolic. On the forty-ninth day, urinalysis showed the slightest possible trace of albumin with rare hyaline and granular casts. Subsequent examinations showed persistent albuminuria with a rare to moderate incidence of hyaline and granular casts. After the forty-ninth day, the dog rapidly became listless and emaciated. He was found dead in his cage on the sixty-second day.

Autopsy, performed from twelve to eighteen hours post mortem, revealed emaciation but otherwise no gross or microscopic abnormalities except in the kidneys. The kidneys, weighing 24 and 23 Gm., appeared small, but normal in shape, with a smooth, reddish-brown surface beneath a slightly adherent capsule. The cut surface showed good differentiation. The cortex measured 8 mm., and the medulla, from 10 to 15 mm. Microscopic sections of the kidney showed marked diffuse, uniform fibrosis throughout with degenerated tubular epithelium and atrophied glomeruli, similar to those found in dog 13. Repair of tubular epithelium was evidenced by the presence of mitotic figures.

DOG 11.—This was a shepherd dog, weighing 14.3 Kg. Radium was injected daily for the first five days, daily from the eleventh to the fourteenth day, again on the forty-first, forty-second, forty-fifth and fifty-fourth days, and finally on the eighty-first day. The total dosage was 154 millicuries, and the experiment lasted eighty-five days.

Within twenty-four hours the leukocyte count dropped from 14,200 to 10,200 per cubic millimeter, and continued to fall gradually until it reached 2,800 per cubic millimeter on the eleventh day, at which it remained until the twenty-first.

and then gradually returned to normal. Following the injections on the forty-first, forty-second, forty-fifth and fifty-fourth days there was a second temporary decrease, with a return to normal by the seventy-fifth day. The final single dose on the eighty-first day again reduced the leukocyte count to 4,240 per cubic millimeter, at which it remained until death.

On the sixty-first day, urinalysis showed a low specific gravity of 1.012 as compared with the previous 1.052, with a slight trace of albumin and rare hyaline casts. Up to this time the dog was in good condition and gained 1.9 Kg.

Definite signs of renal insufficiency appeared on the seventy-first day, the blood urea nitrogen reaching 63 mg. It rose rapidly during the next ten days to 126 mg. just before death. Repeated urinalysis showed persistent low specific gravity with albuminuria and slight cylindruria. The erythrocyte count rose from 5,950,000 to 6,850,000. The blood pressure remained within a normal range, tending to drop during the last thirty days. After the sixty-first day, the dog ate poorly, rapidly lost weight, became progressively weaker and died on the eighty-fifth day.

Autopsy, performed twenty-four hours post mortem, revealed no gross changes except emaciation, dehydration and the abnormally small kidneys, which weighed 25 Gm. each. Autolysis was so far advanced that the microscopic study was valueless.

DOG 12.—This was a shepherd dog, weighing 19 Kg. The active deposit of radium was given intravenously daily for the first eleven days, then four times weekly from the thirty-ninth to the fifty-seventh day—the total dosage being 224 millicuries. The experiment lasted one hundred and six days.

The only early effect of the radium was to produce a marked fall in the leukocytes from approximately 11,000 to 4,400 per cubic millimeter on the ninth day. When the radium was temporarily discontinued, the leukocytes returned to normal by the thirty-fifth day. They again decreased in number when radium was resumed and reached 1,800 per cubic millimeter by the fifty-seventh day.

The first indication of renal insufficiency was the presence of the slightest possible trace of albumin and a rise of blood urea nitrogen to 73 mg. per hundred cubic centimeters on the sixty-third day. At about the same time, the dog refused food and began to lose weight rapidly.

The animal lived forty-three days longer, showing increased albuminuria, cylindruria and oliguria, low specific gravity of the urine and rising blood urea nitrogen, which reached 220 mg. on the day before death. During this time the leukocyte count returned to normal, and the erythrocyte count dropped from 6,180,000 to 4,420,000 per cubic millimeter. There was no significant alteration in the blood pressure. The dog became drowsy, emaciated (losing 6.5 Kg.) and died in collapse on the one hundred and sixth day.

At autopsy, performed immediately, there was marked loss of subcutaneous tissue. The intima of the first portion of the aorta appeared thickened with a few scattered, raised, firm nodules about the size of a pinhead. Histologic sections of the first portion of the aorta, through these nodules, showed scattered focal homogeneous-staining, necrotic areas involving chiefly the media, but extending into the adventitia and intima. Surrounding these areas, the muscle and elastic fibers were condensed as if by pressure from a centrally enlarging lesion. There were numerous smaller areas showing some lymphocytic infiltration, few polymorphonuclears and pigment around the small vessels in the media, with degeneration of the surrounding fibers. The kidneys appeared abnormally small, weighing 22.9 and 26.5 Gm. The capsules stripped with increased difficulty, exposing an irregularly dented, though glistening, surface. On the cut surface, the differentiation was good, with the cortex measuring from 4 to 6 mm. in width. Microscopic

examination of the kidneys showed advanced fibrosis with destruction and replacement of the tubules, hyaline changes in the glomeruli, and marked sclerosis of the small arterioles. Sections of various tissues including the abdominal aorta, iliac arteries and blood vessels in other organs failed to show any pathologic changes.

DOG 13.—This was a terrier, weighing 12.4 Kg. The experiment lasted ninety days. A total of 173 millicuries of the active deposit of radium was administered intravenously in four courses. During the first eight days, seven injections were given in the following doses: 14, 10, 8, 8, 6, 6 and 4 millicuries. The leukocyte count dropped from 10,000 to 5,000 per cubic millimeter on the eighth day; by the twenty-first day it had returned to 7,000. On the fortieth, forty-first and forty-second days, the second course was administered—20, 16 and 22 millicuries, respectively. This produced temporary leukopenia, the count being 2,400. Ten days later, when the count returned to 6,000, the third course, consisting of 14, 7, 12 and 8 millicuries, was given on the fifty-second, fifty-third, fifty-fourth and fifty-sixth days. This again brought the leukocyte count to 2,400 per cubic millimeter. Six days later, the fourth course was given, on the sixty-third, sixty-fourth and sixty-fifth days in doses of 8, 7, and 7 millicuries. The leukocyte count never returned to normal. Repeated counts ranged around 3,000 per cubic millimeter. There was no appreciable effect on the blood pressure. The red blood count increased from 6,210,000 to 7,650,000.

The first indication of renal insufficiency was noted on the seventy-first day in the form of a rise in blood urea nitrogen to 59 mg. Five days later, on the seventy-sixth day, urinalysis showed the specific gravity lowered from 1.060 to 1.012, with the slightest possible trace of albumin and rare to moderate incidence of hyaline and granular casts. These findings persisted in all subsequent specimens. From the sixty-fourth day until death the dog showed a progressive loss of appetite and of weight with increasing weakness and lethargy. The blood urea nitrogen rose to 167 mg. per hundred cubic centimeters. The dog died on the ninetieth day.

Autopsy, performed from twelve to eighteen hours post mortem, revealed marked emaciation and a slight bloody discharge from the nose. The lungs were collapsed, with a patch of consolidation involving a portion of the lower lobe of the left lung. The kidneys were small and uniformly shrunken but normal in shape, weighing 15.5 and 15.6 Gm. The capsules stripped with slightly increased difficulty, exposing a glistening, slightly granular surface. On the cut surface, the markings were well maintained. The cortex measured from 4 to 6 mm. There was no increase in the pelvic fat. The ascending aorta showed scattered, firm, raised nodules. The remaining portions of the aorta were normal. Microscopic examination of the sections through the proximal aorta showed areas of focal degeneration chiefly in the media, similar to those seen in dog 16. The lungs showed moderate congestion, and the section through the consolidated area showed a few scattered polymorphonuclear leukocytes in the alveolar spaces. One medium-sized artery of the spleen revealed a small focal area of degeneration in the media resembling those seen in the aorta. No changes were found in any of the other organs or in their smaller arterioles. Sections of the kidneys were in all respects similar to those found in the preceding dogs of this series.

Table 3 summarizes the findings in the six dogs of series C. The body weights varied between 8.6 and 19 Kg. The average dose of the active deposit of radium was 9 millicuries per kilogram, while the minimum lethal dose was 4 millicuries per kilogram. The duration of life varied directly with the body weight and was inversely proportional to

the dosage of radium. This is well illustrated in dogs 9 and 10, which received approximately the same total dosage. Dog 9 weighed nearly twice as much as dog 10 and lived slightly over twice as long. The average time before signs of renal insufficiency appeared was sixty days; the shortest, thirty-six days. The length of time between the first signs of renal insufficiency and death varied, but was noticeably longer in dog 9, which received the smallest dose. The clinical course was remarkably constant. Leukopenia was consistently an early sign, often appearing within twenty-four hours; there was a slow return to normal when the administration of radium was stopped. The general symptoms, such as anorexia, rapid loss of weight, weakness and apathy, came late and were definitely associated with signs of renal insufficiency. Four dogs actually gained weight during the first few weeks. Four also showed a slight increase in the red blood cells, while in two anemia

TABLE 3.—*Results of Intravenous Injections of Radium in Series C*

Dog	Original Weight, Kg.	Radium Dosage, Mc. per Kg.	Total Mc.	Duration of Administration, Days	Days to Renal Insufficiency	Days from Renal Insufficiency to Death	Average Weight of Kidneys, Gm.
8	18.5	8	163	112	84	28	24.0
9	14.9	4	61	145	64	81	18.0
10	8.6	9	65	62	36	26	23.5
11	14.0	11	154	86	71	11	25.0
12	19.0	12	224	106	63	43	24.0
13	12.5	14	173	90	71	10	15.5

Mc. = millicuries.

developed during the terminal stage. This increase in the red count has been observed previously. Brill and Zehner<sup>14</sup> reported erythrocyte counts as high as 13,000,000 in dogs after administering radium.

Most of the animals died quietly of renal insufficiency without convulsions. One dog collapsed suddenly while being brought from its cage into the laboratory. In all instances there was definite evidence of renal damage and insufficiency, as shown by albuminuria, oliguria, cylindruria, lowered specific gravity and marked retention of blood nitrogen. It is of interest to note that signs of renal insufficiency almost always appeared before albumin or casts could be detected in the urine, although the specific gravity had sometimes fallen previously. Arterial hypertension did not occur. The blood chloride, cholesterol and serum protein values were not appreciably altered except in dog 13, which showed elevated cholesterol. The body temperature remained within normal limits. Gudzent<sup>15</sup> described fever as a symptom of toxic doses

14. Brill, O., and Zehner, L.: *Berl. klin. Wchnschr.* **49**:1261, 1912.

15. Gudzent, F.: *Grundriss zum Studium der Radium Therapie*, Berlin, Urban u. Schwarzenberg, 1919, p. 48.

of radium. In several dogs given radium not included in this study fever developed. Invariably an inflammatory process was found to account for this. These findings confirm the work of Cramer, Drew and Mottram,<sup>16</sup> who pointed out that radium renders the body more susceptible to infection. No edema was noted at any time.

At autopsy, the only outstanding features were emaciation and the remarkably small, uniformly shrunken kidneys. There was a 50 to 75 per cent reduction in the weights of the kidneys as compared to the normal for the same-sized dog. The remainder of the gross examination was persistently negative as to results, except for slight engorgement of the abdominal organs with blood. There were no gross or petechial hemorrhages. No alteration in the bones was noted. Microscopic examination of the heart, aorta (except as mentioned in the protocols of dogs 12 and 13), lungs, liver, spleen, pancreas, stomach and intestines, suprarenal glands, thyroid gland, skeletal muscles, lymph nodes and bone marrow revealed no consistent pathologic changes. Two dogs showed a peculiar focal necrotic area in the middle of the first portion of the aorta. Whether this was accidental or due to radium we do not know. Dog 13 showed in the heart scattered lymphocytic infiltration and a few polymorphonuclears in the interstitial tissues accompanying blood vessels. A section of coronary artery also showed an extensive infiltration by polymorphonuclears and lymphocytes involving chiefly the media and adventitia and, to a lesser extent, the intima. These changes are probably not related to the radium. The lungs showed varying degrees of edema and congestion. One dog (13) showed a small area of bronchopneumonia, but in no case was there frank lobar pneumonia. The kidneys, however, showed consistent histologic changes, which were remarkably constant and varied but slightly in severity. The dogs that lived the longest showed the most abnormality. These changes consisted of hyalinization and thickening of the glomerular tuft arterioles with tuft vessels devoid of blood, fibrous thickening of Bowman's capsules, marked tubular degeneration and marked diffuse fibrosis. Frozen sections stained with scarlet red showed deposits of fat restricted to the convoluted tubules. Slight thickening of the arterioles outside of the glomeruli was present with comparatively little change in the larger vessels.

#### IV. ELIMINATION OF THE ACTIVE DEPOSIT OF RADIUM EMANATION

In the preceding experiments, the dogs showed the changes in the blood described by numerous investigators as characteristic of an effect of radium. We were much surprised at autopsy to find so little change

16. Cramer, W.; Drew, A. H., and Mottram, S. C.: Proc. Roy. Soc. London, s. B, **93**:449, 1922.

in organs other than the kidneys. The following elimination experiments were undertaken to explain why the kidneys were the only organs in which functional and pathologic changes were found.

Extensive studies have been made on the elimination of soluble and insoluble radium salts.<sup>17</sup> According to Smith,<sup>17</sup> radium emanation in solution is eliminated almost entirely by the lungs and to a slight extent by the kidneys and is complete in four hours. There is little reference in the literature to the elimination of so-called "short-lived radium products" or "the active deposit of quick change."

Bagg<sup>5</sup> in 1921 tested the organs for radioactivity shortly after intravenous injection of the active deposit of radium emanation. He found the greatest amount in the liver, and the next greatest amount in the stomach and gastro-intestinal tract. Both kidneys contained one-third

TABLE 4.—*Radioactivity of 30 Gm. of Each of Various Organs of Dogs 16 and 17 Killed One-Half Hour and Two Hours, Respectively, After a Single Intravenous Injection of 35 Millicuries and 50 Millicuries of the Active Deposit of Radium*

Organ—30 Gm.	Dog 16—Killed at One-Half Hour			Dog 17—Killed at 2 Hours		
	Time for Ten Divisions		Divisions per Second	Time for Ten Divisions		Divisions per Second
	Min.	Sec.		Min.	Sec.	
Leak of gold leaf at start	10	50	0.015	3	30.8	0.0473
Left kidney	0	3	3.57	1	37.2	0.103
Right kidney	0	2.8	3.54	1	27.6	0.114
Spleen	0	28	0.361	0	17.8	0.0726
Liver	0	33.6	0.298	3	16	0.051
Bone	0	37	0.270	3	22	0.049
Lung	0	41.4	0.242	3	28	0.0481
Heart	1	46	0.0943	3	31	0.04744
Leak at finish	12	30	0.013	3	31.4	0.04734

as much as the liver. The lungs showed less than one-half as much as the kidneys, while the spleen showed less than the lungs.

*Procedure.*—Four dogs (series D) were given single intravenous injections (4 millicuries per kilogram) of radium. The whole body of the animal and specimens of blood and urine were tested for radioactivity at one-half hour intervals with the Lind electroscope.<sup>18</sup> The animals were killed at one-half, two, three and four hours, respectively.

Equal amounts (30 Gm.) of the various organs, including the heart, lungs, bone, spleen, liver and kidneys, were then tested as soon as possible with the electroscope.

Radioactivity of the animal bodies could be detected with the electroscope in decreasing amounts during the first three hours only. The blood was found to be radioactive, and the activity decreased with each

17. Smith, Bellingham E.: Quart. J. Med. 5:249, 1912. Seil, Viol C., and Gordon, M.: New York M. J. 101:896, 1915.

18. Schlundt, H.; Barker, H., and Flinn, F.: Am. J. Roentgenol. 21:345, 1929.

succeeding specimen, until at the end of two hours only a very minute amount could be detected. The urine was found to be radioactive at the end of thirty minutes. This activity increased during the first two hours, then rapidly decreased.

The organs, including the kidneys, of the dog killed at the end of four hours, showed no measurable amount of radioactivity. In the dog killed at three hours, the kidneys were the only organs showing any measurable amount of radioactivity.

However, the organs of the two dogs killed at two hours and one-half hour, respectively, showed interesting results, summarized in table 4. It will be seen that in both cases the kidneys showed, per gram of tissue tested, relatively more deposited activity than any of the other organs. The spleen was second, the liver third, the bone fourth and the lungs fifth, while the heart in both cases showed the least.

These experiments show that during the first two hours following intravenous injection of the active deposit of radium, a relatively large part is present in the kidney. The decrease in the radioactivity of the blood and the progressive increase in that of the urine suggest that the kidney plays a prominent rôle in its excretion. The evidence suggests that the radioactive substance is at first widely distributed throughout the body, and that its effect in small doses is transient and therefore probably noninjurious except in the kidney, where its effects are concentrated during the process of elimination. This conclusion is supported by the previous experiment in which a single dose was injected into one renal artery. In this experiment, the kidneys were the only organs showing pathologic changes, and these were most marked in the kidney receiving the injection.

#### SUMMARY AND CONCLUSIONS

Chronic renal insufficiency without hypertension has been consistently produced in dogs by intravenous injection of the active deposit of radium emanation. The length of life varied inversely with the dosage of radium.

The kidneys were the only organs showing pathologic or functional change. This apparent selective action is probably due to the excretion of the active deposit of radium by the kidneys, resulting in a greater concentration of radioactivity in these organs. The kidneys were uniformly small and contracted, showing glomerular, tubular, interstitial and vascular changes comparable in some respects to what occurs in man in chronic hypertensive nephritis. No hypertension was produced, however.

A study of the nature and progression of the renal lesion was made. The earliest detectable change occurred thirty days after the initial dose

of radium and consisted of hyaline changes in the arterioles of the glomerular tufts and a spotty degeneration of the tubular epithelium. In addition, early swelling of the tubular basement membranes was observed. The fact that the cells of the tubular epithelium, during the early stages of the lesion, showed the presence of mitotic figures (i. e., an attempt at regeneration) suggests that the destruction of the tubules is largely secondary to the action of the radium on the cement and collagen substances throughout the kidney. Subsequently these changes became progressively more marked, eventually leading to great tubular destruction with connective tissue replacement and contraction. While the glomeruli showed definite hyalinization and thickening of the capsule and the capillary tuft walls, the lesion was much less marked in them than in the tubules.

## EFFECT OF CINCHOPHEN ON THE ALBINIC RAT

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BROOKLYN

Untoward effects from cinchophen have been reported increasingly, since 1923. Various types of toxic symptoms have been ascribed to the drug. Representative reports are those by Schroeder,<sup>1</sup> Klinkert,<sup>2</sup> Schwahn,<sup>3</sup> Worster-Drought,<sup>4</sup> Rabinowitz,<sup>5</sup> Willcox,<sup>6</sup> Motzfeldt,<sup>7</sup> Dassen,<sup>8</sup> de Rezende,<sup>9</sup> Loewenthal, Mackay and Lowe<sup>10</sup> and others. An anaphylactoid reaction has been recorded by Scully.<sup>11</sup> When deaths have occurred and pathologic changes have been found in the liver, these have been imputed by a method of reverse reasoning to cinchophen. Usually the hepatic lesion consisted of extensive parenchymal necrosis resembling that in acute yellow atrophy. Brugsch and Horsters,<sup>12</sup> and Horsters,<sup>13</sup> in demonstrating a choleric action for cinchophen, ascribed this action to a direct effect on cells of the liver, stamping it as a potential protoplasmic poison.

Rabinowitz's<sup>5</sup> review of cinchophen poisoning stimulated experimental investigations to determine any causative relationship between cinchophen and hepatic damage. Churchill and Van Wagoner<sup>14</sup>

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1. Schroeder, K.: Ugesk. f. læger. **84**:1141, 1922.
2. Klinkert, D.: Nederl. tijdschr. v. geneesk. **70**:1963, 1926.
3. Schwahn, W.: Klin. Wchnschr. **3**:935, 1924.
4. Worster-Drought, C.: Brit. M. J. **1**:148, 1923.
5. Rabinowitz, M. A.: M. Clin. North America **11**:1025, 1928; J. A. M. A. **95**:1228, 1930.
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7. Motzfeldt, K.: Norsk mag. f. lægevidensk. **90**:217, 1929.
8. Dassen, R.: Semana méd. **36**:368, 1929.
9. de Rezende, C.: Ars méd., Barcelona **3**:253, 1927.
10. Loewenthal, L. J. A.; Mackay, W. A., and Lowe, E. C.: Brit. M. J. **1**:592, 1928.
11. Scully, F. J.: J. A. M. A. **82**:623, 1924.
12. Brugsch, T., and Horsters, H.: Ztschr. f. d. ges. exper. Med. **38**:267, 1923; **43**:517, 1924; Med. Klin. **20**:661, 1924.
13. Horsters, H.: Arch. f. exper. Path. u. Pharmakol. **105**:11, 1925.
14. Churchill, T. P., and Van Wagoner, F. H.: Proc. Soc. Exper. Biol. & Med. **28**:581, 1931.

produced necrosis of the liver in dogs by oral administration of cinchophen, using twenty-seven times the usual therapeutic dose. They found a concomitant increased retention of bromsulphalein, implying a lowering of hepatic function. Recently Reichle<sup>15</sup> concluded that cinchophen did not induce hepatic cirrhosis in white rats. Myers and Goodman<sup>16</sup> called attention to mild cytologic changes in the liver following oral administration of cinchophen to dogs and rabbits over short periods of time. The changes which they described have frequently been noted, however, in animals not given any drug, as well as in those receiving cinchophen. They concluded that cinchophen exerts a toxic action on the liver.

For the past two years we have studied effects of cinchophen in rats.

#### LETHAL DOSE

The lethal dose of cinchophen was first determined. Each of six rats, weighing approximately 200 Gm. was given an intramuscular injection of 1 cc. of a sterile solution of sodium cinchophen, 0.5 Gm., and beta-eucain lactate, 0.0073 Gm., in 5 cc. of distilled water. This dose was equivalent to 0.5 Gm. per kilogram of body weight. One of the animals died in 10 hours and another in 12 hours. Eighteen hours after the first injection, a second dose of 1 cc. of the drug was given to each of the four surviving animals. Two of the latter died in 2 hours and the remaining two in 6 hours. Thus, all the animals died within 24 hours as the result of the administration of from 0.5 to 1 Gm. of cinchophen per kilogram of body weight. For some time before death they showed marked evidences of toxicity, and all died in coma. On autopsy, the lungs of the first animal to die showed many abscesses. The organs of the other animals showed no characteristic changes, except for marked congestion. The architecture of the liver was intact; the cells and nuclei appeared normal.

#### INFLUENCE OF DIET ON EFFECT OF CINCHOPHEN

*Normal Diet.*—Twenty-eight normal male albino rats, each weighing approximately 250 Gm., were maintained on the following normal diet:

	Per Cent
Yellow corn meal .....	50
Linseed oil meal .....	15
Crude casein .....	5
Ground alfalfa .....	2
Dextrimaltose with vitamin B .....	5
Powdered whole milk .....	20
Cod liver oil .....	2
Sodium chloride and calcium carbonate .....	0.5 each

15. Reichle, H. S.: Arch. Int. Med. **49**:215, 1932.

16. Myers, H. B., and Goodman, L.: Arch. Int. Med. **49**:946, 1932.

There were five groups of five rats each and one group of three rats. One group was given daily intramuscular injections of a soluble derivative of cinchophen, the dose being equivalent to the average human dose per kilogram of body weight. A second group was given twice that dose, and so on, but the last three rats were given seven and a half times the human dose. Aseptic technic was employed. The animals were weighed at regular intervals and their general condition noted. All the animals in the last three groups failed to finish their food, became listless and appeared ill. Some became gaunt, their fur stood erect, and most developed a marked pallor. Many lost weight. None gained as rapidly as the controls. These toxic symptoms subsequently appeared also in some of the animals receiving the smaller doses. At the end of 125 days, the sickest animal in each group was put to death. At the same time, a normal animal on the stock diet that had not received cinchophen was killed as a control. This procedure was repeated at 140, 154, 169 and 180 days, until all the animals had been killed. An immediate autopsy was made on each animal.

Autopsy disclosed no infections at the sites of injection. No characteristic gross lesion was found, except an occasional pulmonary abscess. Microscopically, there were focal necroses of the liver, varying from mere collections of polymorphonuclear leukocytes to areas of complete parenchymal destruction, usually delimited by a border of fibrous tissue. Occasionally there was acute hepatitis with fatty and hydropic degeneration and hemorrhage, showing a predilection for the periphery of the lobule. In most of the other livers there were marked cloudy swelling, granulation of cells and round cell infiltration. Hepatitis or focal necroses were found in twelve of the twenty-eight animals. Eleven of the others showed marked cloudy swelling and round cell infiltration, while five were apparently normal. In one of the five controls focal necroses were found, but without diffuse hepatitis.

*Low Carbohydrate Diet.*—In 1915, Opie and Alford<sup>17</sup> demonstrated the protective effect of a carbohydrate diet of oats and cane sugar against hepatic poisons such as chloroform, uranium nitrate and potassium chromate. To determine the effect of a low carbohydrate diet on the action of cinchophen, the following procedure was adopted: Fifteen rats weighing about 250 Gm. each were starved for 3 days, which is at least 24 hours longer than is generally agreed to be necessary to deplete the liver of most of its available glycogen.<sup>18</sup> The following diet was

17. Opie, E., and Alford, L. B.: *J. Exper. Med.* **21**:1, 1915.

18. Cori, C. F.: *Proc. Soc. Exper. Biol. & Med.* **23**:286, 1925-1926; Harvey Lectures, Philadelphia, J. B. Lippincott Company, 1925-1926, p. 286. Cori, C. F., Cori, G. T., and Pucher, G. W.: *J. Pharm. & Exper. Therap.* **21**:377, 1923.

then given in small rations of 8 Gm. per animal per day to insure a consistent loss of weight:

	Per Cent
Casein .....	30
Gluten .....	30
Linseed oil meal .....	20
Alfalfa .....	2
Powdered whole milk .....	13
Dextrimaltose with vitamin B.....	2
Cod liver oil .....	2
Sodium chloride and calcium carbonate.....	0.5 each

Ten animals were given daily intramuscular injections of a cinchophen preparation gradually working up to ten times the human dose. The animals given cinchophen shortly failed to empty their food cans, while the controls on the same measured diet finished theirs rapidly. Signs of illness soon supervened, more severe than in the preceding experiment. The animals were killed when death seemed imminent, the first rat after 13 days, the last after 41 days. The five controls lost weight, but remained active and vigorous, and were killed at comparable intervals.

On autopsy there was no gross evidence of damage. Microscopically, a picture was encountered similar to that found previously. Four of the ten animals presented diffuse hepatitis or focal necroses. The other six showed swelling and irregularity of cells, indistinctness of cell outline and irregularity of nuclear staining. The controls presented no abnormalities. These effects had come on in less time than had been required with animals on normal diets, and the symptoms were much more severe.

*High Carbohydrate Diet.*—Five rats were placed on liberal rations of a diet high in carbohydrate as follows:

	Per Cent
Corn meal .....	75
Dextrimaltose with vitamin B.....	10
Alfalfa .....	2
Powdered whole milk .....	10
Cod liver oil .....	2
Sodium chloride and calcium carbonate.....	0.5 each

These rats also were given cinchophen intramuscularly in increasing daily doses until seven and a half times the human dose was reached. The latter dose was continued until all the animals had been put to death. Three controls were given the same diet, but no cinchophen. All the animals given cinchophen gained weight and were fairly active, although not so much as the controls. None were ever moribund as in the previous experiments. The first rat was killed after 73 days; the last, after 135 days. The controls were killed at similar intervals.

On autopsy, the liver of one of the animals given cinchophen showed focal necroses. Another animal, with an infection of the fore leg, showed severe granular degeneration, cellular swelling and an extensive area of massive degeneration of the parenchyma of the liver. One other showed extensive cloudy swelling. The other two were apparently normal. There were no material changes in the other viscera. The controls showed no pathologic changes.

#### INFLUENCE OF INFECTION

There were in stock forty-five animals that were apparently ill. On nine of these, chosen at random, autopsies were made. All showed marked pulmonary lesions, varying from consolidation of a lobe to multiple abscesses. The remaining animals, two groups of eighteen rats each, were maintained under similar conditions, but to one group cinchophen was given as in previous experiments. After 39 days the first rats were put to death; the last, after 101 days. The maximum dose was 0.4 Gm. per kilogram. The controls were fairly active and vigorous and made consistent gains, but the animals given cinchophen shortly began to show signs of severe toxemia.

On autopsy, all the animals showed severe pulmonary lesions grossly, as described. The other organs seemed normal. On microscopic section, seven of the eighteen animals given cinchophen and eight of the eighteen controls showed the same picture in the liver—fatty and hydropic degeneration, particularly about the central vein, with round cell and polymorphonuclear infiltration. The remaining eleven of the animals given cinchophen showed no marked lesion of the liver. None of the controls suffered the severe toxic symptoms that were encountered in the animals given cinchophen.

#### BACTERIOLOGIC OBSERVATIONS IN RELATION TO EFFECT OF CINCHOPHEN

An attempt was made to ascertain to what extent factors other than cinchophen were responsible for the changes in the liver found in the preceding experiments. Fourteen normal animals weighing 125 Gm. each were given cinchophen as previously. Fourteen similar animals acted as controls. Both groups were given a normal diet. Ten other animals, each weighing approximately 200 Gm., were starved for 3 days, then given the same low carbohydrate diet with rations of 8 Gm. per rat, as in the experiment with a low carbohydrate diet described in earlier paragraphs. Five of the latter were also given cinchophen. The animals on normal diet were put to death after from 48 to 120 days. The animals on the low carbohydrate diet were put to death after from 29 to 94 days. Toxic manifestations were encountered in all the animals receiving the drug, although more severe in those on the low carbo-

hydrate diet. After each animal was killed, the abdomen was immediately opened under sterile precautions, and cultures were taken from the liver and spleen.<sup>19</sup> Simultaneously, blood agar plates were poured, 1 cc. of cardiac blood being used. Cultures were made in the same manner from the last six animals, but with anaerobic as well as aerobic technic. *Bacillus coli* was the only organism recovered, and in but a few instances, even with anaerobic methods. Many cultures were sterile. When a growth occurred, the organism was identified by fermentation of sugars.

Autopsy revealed no marked gross changes. On microscopic examination, however, thirteen of the fourteen animals on normal diet that were treated with cinchophen showed severe degrees of focal necrosis or hepatitis. Of the fourteen controls, one showed two areas of focal necrosis. Of the animals on a low carbohydrate diet which were given cinchophen two showed severe lesions of the liver, as did two of the controls. The presence of changes in the liver did not necessarily coincide with the finding of a positive culture.

OBSERVATIONS FOLLOWING ADMINISTRATION OF BETA-EUCAIN  
LACTATE

To rule out the possibility that the toxic symptoms might be caused by the other constituent of the cinchophen preparation, i. e., beta-eucain lactate, eight animals averaging 100 Gm. each, on a normal diet, were given an injection of an amount of beta-eucain lactate equivalent to that contained in a lethal dose of the cinchophen preparation. There was no discernible effect. The dose was repeated daily for one month, after which all the animals were killed. They had gained weight as well as the stock animals and were active and well. Cultures taken from the spleen, liver and blood of these animals, aerobically and anaerobically, revealed *B. coli* in the liver in five cases, but the livers as well as the other organs appeared normal, both grossly and microscopically.

COMMENT

That cinchophen used over a long period of time in sublethal doses produces toxic effects on the organism cannot be doubted from these experiments. Whether cinchophen in sufficient dosage to be toxic produces changes in the liver of the rat comparable to the necrosis or the acute yellow atrophy of the liver in man is another question. Although a lesion was repeatedly found in animals receiving the drug, it cannot be definitely ascribed to cinchophen. Such a lesion can be caused by

19. A surface of the organ was seared by a hot glass rod, a platinum loop plunged into the body of the organ, and the tissue thus withdrawn streaked on Endo plates and introduced into dextrose broth.

any of the infections to which rodents are susceptible. When similar changes were found in a control animal, however, they were few in number and not so severe. The mild cellular changes seen in many of the livers were nonspecific and referable to a variety of extraneous factors.

To summarize: Exclusive of the animals in the infected series, sixty-two rats were given cinchophen, and forty were maintained on similar diets, under the same conditions, as controls. Of the sixty-two rats given cinchophen, 33, or approximately 53 per cent, showed severe damage of the liver. Of the forty controls, only four, or 10 per cent, showed the same changes. In the latter group, the lesions were not accompanied by symptoms of toxemia.

Although these changes are not characteristic of cinchophen, their marked preponderance in the animals receiving the drug does not allow them to be dismissed as coincidental. The controls had been maintained under conditions identical with those under which the animals receiving cinchophen were kept. They suggest, therefore, a definite although indirect causative bearing. While the drug does not produce a characteristic lesion in the rodent liver, it appears to render it more susceptible to damage. Moreover, this action seems to be confined to the liver. These effects cannot be ascribed to lowering of resistance from frequent handling and daily injections, because controls receiving daily injections of beta-eucain lactate apparently suffered no ill effects. We therefore characterize the hepatic changes as an index of damage to the liver.

Without the coincident presence of toxemia, changes in the liver cannot be assigned any significance. When controls presented lesions of the liver, there were no associated toxic symptoms. At times, animals receiving large doses of cinchophen were highly toxic without showing pathologic changes in the liver.

In animals on semistarvation rations of a diet low in carbohydrate, toxic symptoms became severe in a very short time. No cases of severe toxemia existed in animals on a diet high in carbohydrate. The bearing which this has on the administration of the drug in severe states of malnutrition is evident.

When palpably infected animals were given cinchophen, there was no increase in the incidence of hepatic changes, nor was there a decrease in the time required for toxic symptoms to eventuate.

#### CONCLUSION

The lethal dose of cinchophen for the white rat is from 0.5 to 1 Gm. per kilogram of body weight.

Cinchophen given in small doses gradually increased to ten times the human dose initiates toxic symptoms in the white rat, the larger doses being more effective.

Cinchophen does not produce a characteristic lesion of the liver in white rats, but acts on the liver by lowering its resistance to hepatotoxins.

Pulmonary infection does not predispose the liver to more severe intoxication from cinchophen.

Toxicity from cinchophen occurs more easily in animals on a diet low in carbohydrate, in a poor state of nutrition, than in those on a diet high in carbohydrate, in a good state of nutrition.

The effects of cinchophen other than its toxic action on the liver require further study. Whether the drug ever produces a characteristic lesion of the liver in man still remains a mooted point.

## RETICULUM IN TUMORS

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AND

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We have examined the distribution of reticulum in carcinomas to determine whether or not any relationship exists between the reticulum content and the degree of malignancy. Our index of malignancy is the one developed by Broders,<sup>1</sup> in which the proportion of differentiated to undifferentiated cells in a tumor is estimated. If the differentiated cells comprise 75 per cent or more of the tumor, it is graded 1; if from 50 to 75 per cent of the tumor, it is graded 2; if from 25 to 50 per cent of the tumor, it is graded 3, and if the differentiated cells make up less than 25 per cent of the tumor, the undifferentiated cells comprising the remaining 75 per cent or more, it is graded 4. Broders, Jorstad<sup>2</sup> and others who have considered the problem have stated that the grade of malignancy is a reliable index of the clinical course of the tumor. There has developed a not inconsiderable conflict of opinion regarding the accuracy, dependability and prognostic value of grading. Melnick,<sup>3</sup> among other investigators, stressed this point. In view of this, we sought to determine whether or not a detailed study of reticulum would furnish an additional factor in an analysis of the relationship existing between tumor morphology and tumor growth. With this thought in mind, we availed ourselves of the opportunity to study the distribution of reticulum in tumors, which had previously been independently studied histologically and graded by Dr. Louis H. Jorstad, pathologist at the Barnard Free Skin and Cancer Hospital, of St. Louis.

### REVIEW OF CURRENT LITERATURE

The first extensive published researches concerning reticulum appeared in 1857, when Billroth announced, after study of the reticulum of the spleen, that this tissue was composed of anastomosing, branching cells, containing but few nuclei. Contemporaries of Billroth, Donders and von Koelliker were early students of reticular tissue, which was so named by von Koelliker because of its reticulated appearance.

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From the Research Department of the Barnard Free Skin and Cancer Hospital.

1. Broders, A. C.: Bull. Am. Soc. Control Cancer **14**:1, 1932.
2. Jorstad, L. H.: J. Cancer Research **14**:295, 1930.
3. Melnick, P. J.: Am. J. Cancer **16**:890, 1932.

Henle, in 1859, announced that reticulum was not a cellular structure, but was made up of fibrils of varying thickness, forming a network. Henle taught that reticulum was not a special kind of connective tissue, but that all connective tissue was composed of varying concentrations of reticular fibers. Henle's idea regarding the fibrillar character of reticulum was firmly established by the researches of Ranvier, Bizzozero, Mall, Spalteholz and Hoehle. His disagreed with Henle's ideas that all forms of connective tissue were merely varying arrangements of reticular fibrils, and he undertook some chemical studies to prove his opinions. However, it was the work of Mall<sup>4</sup> which definitely established the differences between white fibrous tissue, elastic tissue and reticulum through their varying reactions to the digestive action of pancreatin, acids and alkalis. All the early work that has been cited here is well summarized in a collective abstract published by Disse in 1897.<sup>5</sup> By developing a technic of silver impregnation of nerve fibers, Bielschowsky, in 1905, offered a new method for the study of reticulum, which was based on the fact that this tissue is argyrophilic.<sup>6</sup> Numerous modifications of this method have been perfected and have been a stimulus for renewed interest in this tissue.

The origin of connective tissue is still in dispute. Observations in the embryo by Baitsell<sup>7</sup> indicate that it may appear even before the mesenchymal cells can be detected, and probably is a secretion of the cells of the various germ layers. Maximow,<sup>8</sup> in 1928, and McKinney,<sup>9</sup> working later in his laboratory, observed in tissue cultures the formation of argyrophilic fibers in the zone of new growth, developing directly from the preformed reticulum of the explant. By the fifth day of culture, the fine network of reticulum had become coarser, losing its silver staining property and taking on the fuchsin stain of collagen, thus indicating a definite transformation of the reticulum into the collagen. Miller<sup>10</sup> described, as one method of scar formation in tubercles, the transformation of reticulum into fibrous tissue. The reticulum, thus transformed, always was produced by an outgrowth from reticulum which was normally present in the tissue. Foot,<sup>11</sup> in cultures of rabbit leukocytes, observed the formation of a reticular

4. Mall, F. B.: Johns Hopkins Hosp. Rep. **1**:171, 1896.
5. Disse, J.: *Ergebn. d. Anat. u. Entwickelungsgesch.* **7**:9, 1897.
6. Bielschowsky, Max: *Arch. f. Psychiat.* **39**:1321, 1905; *J. f. Psychol. u. Neurol.* **12**:135, 1908.
7. Baitsell, G. A.: *Quart. J. Micr. Sc.* **69**:571, 1925.
8. Maximow, A.: *Proc. Soc. Exper. Biol. & Med.* **25**:439, 1928; *Centralbl. f. allg. Path. u. path. Anat.* **43**:145, 1928. Maximow, A., and Bloom, William: *Ztschr. f. mikr.-anat. Forsch.* **17**:625, 1929.
9. McKinney, R. L.: *Arch. f. exper. Zellforsch.* **9**:14, 1930.
10. Miller, W. S.: *Am. Rev. Tuberc.* **7**:141, 1923.
11. Foot, N. C.: *Am. J. Path.* **3**:401, 1927.

network from the reticulum of laked blood. In 1927, Mallory and Parker<sup>12</sup> expressed the opinion that reticulum and collagen are identical histologically, but that the former retains the silver particles because of a finer dispersion of fibrillar substance. Thus, these men reiterated the idea held by Henle of the unity of the connective tissue. Foot<sup>13</sup> disagreed with Mallory and Parker, and showed by chemical studies the distinct difference between collagen and reticulin, but suggested that the reticulin may be hydrolyzed to form collagen.

In 1920, Corner<sup>14</sup> stressed the almost universal association of reticulum with endothelial cells. He concluded that reticulum is produced by the capillary endothelium. Rinehart<sup>15</sup> studied the differentiation of fibrous tissue in the mesenchyme, and asserted that this is accomplished by a realinement of cells and fibrillar substance, accompanied by a change in the silver impregnating reaction. Capillaries and lymphatics are formed as simple clefts, *in situ*, in the mesenchyme, the cells and fibers becoming flattened and forming the lining endothelium of these spaces. Epithelial structures in their development invade the mesenchyme, and a layer of mesenchymal cells is applied to the periphery of these structures to form a basement membrane. Rinehart was able to demonstrate reticulum in the capillary endothelium of all embryonic and adult organs and tissues.

Several investigators have studied the distribution of reticulum in tumors. In 1907, one of us (M. G. S.<sup>16</sup>), applying the pancreatin digestion method of Mall, studied the configuration of reticulum in lymphosarcomas and round cell sarcomas. The main conclusions drawn from this study were (1) that the quantity of reticulum present in lymphosarcomas and round cell sarcomas varies within such broad limits and with such irregularity as to make it impossible to differentiate these two tumors on the basis of reticulum content; (2) that the configuration of the reticulum found in the two types of tumor (lymphosarcoma and round cell sarcoma) was striking, but not specifically characteristic and not necessarily similar to the architecture of the reticulum of the organ occupied by the tumor. Foot and Day,<sup>17</sup> although they found that reticulum is usually more abundant in young and rapidly growing tumors than in those of adult type and slower growth, concluded that there was no constant connection between the rate of tumor growth and the reticulum content. They also failed to find any definite relationship between cellular structures and reticulum, which

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12. Mallory, F. B., and Parker, F., Jr.: Am. J. Path. **3**:515, 1927.
13. Foot, N. C.: Am. J. Path. **4**:525, 1928.
14. Corner, G. W.: Contrib. Embryol. **9**:85, 1920.
15. Rinehart, J. F.: Am. J. Path. **6**:525, 1930.
16. Seelig, M. G.: Surg., Gynec. & Obst. **4**:319, 1907.
17. Foot, N. C., and Day, H. A.: Am. J. Path. **1**:431, 1925.

was found to be quite as abundant in the proximity of epithelial cell masses as it was near endothelial or fibroblastic cells. They found reticulum to be more abundant in endothelial tumors, and emphasized that, in tumors of the reticulo-endothelial system (e. g., endothelioma), the amount and character of the reticulum may be a differentiating point, distinguishing tumors of endothelial origin from those of epithelial origin. In carcinoma, the reticulum usually lies at the periphery of the cell nests, though it may penetrate the nests in straight, fragmented lines from the periphery; in contrast with this arrangement, there are in endotheliomas, abundant branching plexuses of curving reticular fibrils intimately associated with the cells of the tumor. Speciale<sup>18</sup> reached similar conclusions.

#### MATERIAL AND METHODS

The material for our study was obtained from the surgical service of the Barnard Free Skin and Cancer Hospital. The majority of the tumors were routine surgical specimens. The tissue was fixed in formaldehyde, sectioned and stained with hematoxylin and eosin. Duplicate slides, cut from the same block were stained for reticulum, the study of which forms the basis of this report. About twenty-five additional tumors were obtained at the time of operation, *directly from the operating table*, and were fixed at once in Bouin's solution, embedded in paraffin and stained for reticulum. The technic of preparing this group for silver impregnation was carefully done with the hope of securing optimum conditions for staining. Duplicate control sections of this material were stained with hematoxylin and eosin for the purpose of grading them. Whether or not the technic of fixation and embedding played a part, it was observed that the silver staining technic for reticulum gave much better results in this set of specimens that were fixed immediately at the operating table. The tissues that were subjected to the ordinary laboratory technic frequently showed silver precipitation, which in many instances rather obscured the distribution of reticulum.

The tumors studied were obtained from the skin, face, tongue, lip, esophagus, rectum, breast, and cervix and body of the uterus. In addition, several tar cancers of the skin of mice, one of these being metastatic to the lung, were examined. Histologically, most of the tumors were squamous cell carcinomas. There were several adenocarcinomas, two of which were colloid, and a few epitheliomas identified histologically as cystic basal cell carcinomas. As we have already stated, each tumor was independently graded by Dr. L. H. Jorstad, director of the pathologic laboratory. This grading is used in our report.

18. Speciale, N.: *Tumori* **10**:37, 1923.

The technic that we followed in staining was the one described by Foot,<sup>19</sup> consisting essentially of an impregnation of the section in a warm silver ammonium carbonate bath, counterstaining with the Harris hematoxylin-van Gieson stain. The reticulum takes the silver stain and appears in the tissue as a fine, black-staining, wavy, dendritic network. The collagen takes the red or pink color of fuchsin; muscle takes a color varying from yellow to orange and the cell nuclei become purplish. In well stained preparations the reticulum stands out strikingly against the background of stroma and parenchyma.

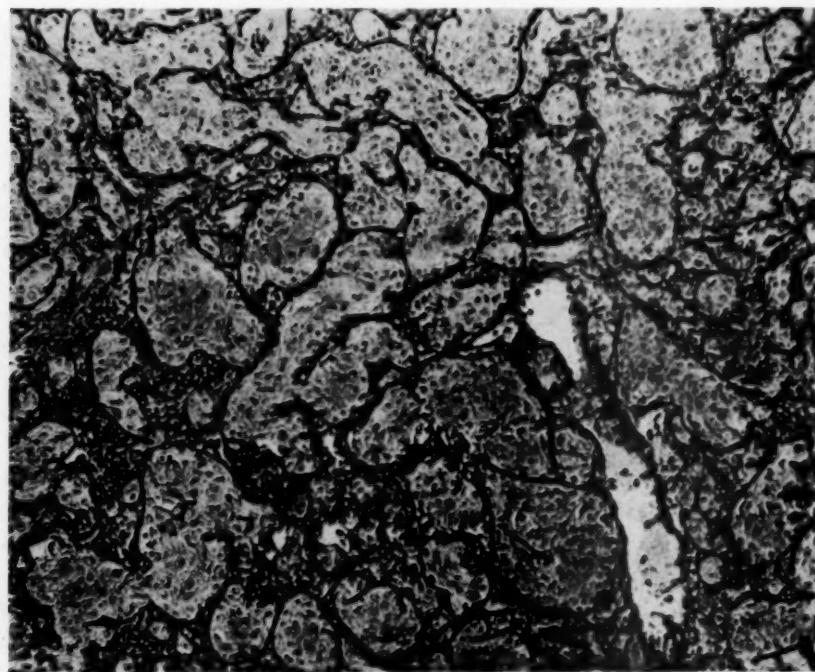


Fig. 1.—Squamous cell carcinoma of buccal mucous membrane (grade 3), showing distribution of reticulum around epithelial cell nests;  $\times 125$ .

#### RETICULUM IN THE STROMA

Reticulum ramifies through the stroma of tumors. Where tubular or acinar structures of normal character are present, a fine layer of reticulum is closely applied to the periphery of each tubule, circumscribing it as a basement membrane. In general, malignant epithelial nests, acini and tubules are surrounded by a similar membrane of reticulum (fig. 1), although there are exceptional instances in which

19. Foot, N. C., and Menard, M. C.: Arch. Path. 4:211, 1927.

this arrangement does not exist. It is possible to demonstrate a layer of reticulum at the periphery of the capillary endothelium, and in many instances these same fibers are apparently continuous with the layers outlining the parenchymatous cells (figs. 2 and 3). Between the epithelial nests, the reticulum is distributed in the stroma as a fine network, its character and abundance depending on the nature of the stroma.

Reticulum was abundant in the stroma of the tumors growing in lymph nodes, intestine and muscle tissue, notably in the tongue and uterus. It was not abundant in the stroma of tumors of the skin. In the stroma of tumors of the breast, the reticulum content was vari-

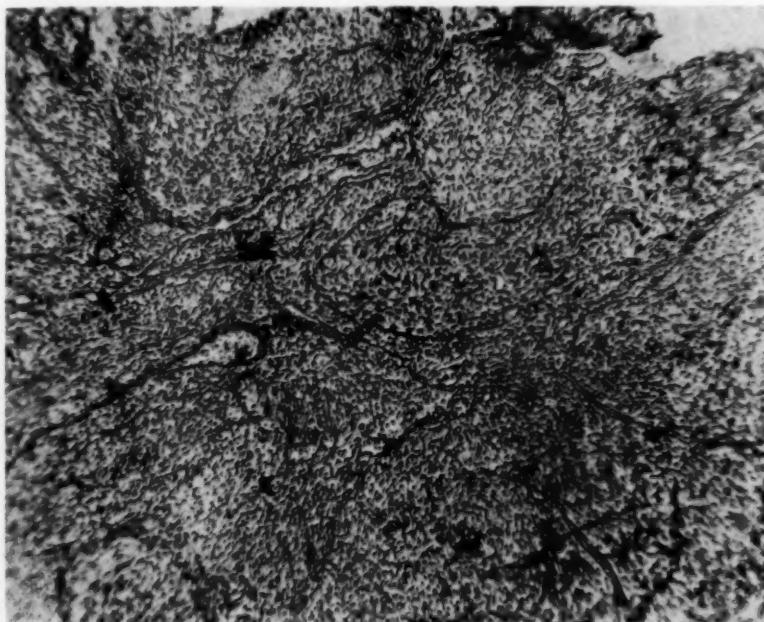


Fig. 2.—Adenocarcinoma of the lower lid (grade 3), showing distribution of reticulum around epithelial cell nests and capillary endothelium;  $\times 62$ .

able, depending on the amount of dense connective tissue present. These observations seem to indicate that the normal reticulum content of a tissue determines in large part its presence in a tumor of and in that tissue. As normal tissue is invaded by a new growth, the tissue reticulum which escapes destruction becomes an intricate part of the tumor. Under these circumstances it is probable that to a large extent new formed reticulum is an outgrowth from preformed reticulum, if we are correct in interpreting the formation of reticulum in tumors on the basis of our knowledge of its formation under other normal and pathologic circumstances.

It was observed during the study of the various tumors of our series that there were several distinctly different types of stromas. These may be classified as follows: (1) thin, areolar stroma, either scanty in amount, serving as a support and as a vascular framework for the very large and numerous parenchymatous nests which make up most of the tumor, or abundant in amount, comprising the greater part of the tumor, filling in the spaces between small epithelial nests and acini; (2) fibroblastic stroma, consisting of growing fibroblasts and

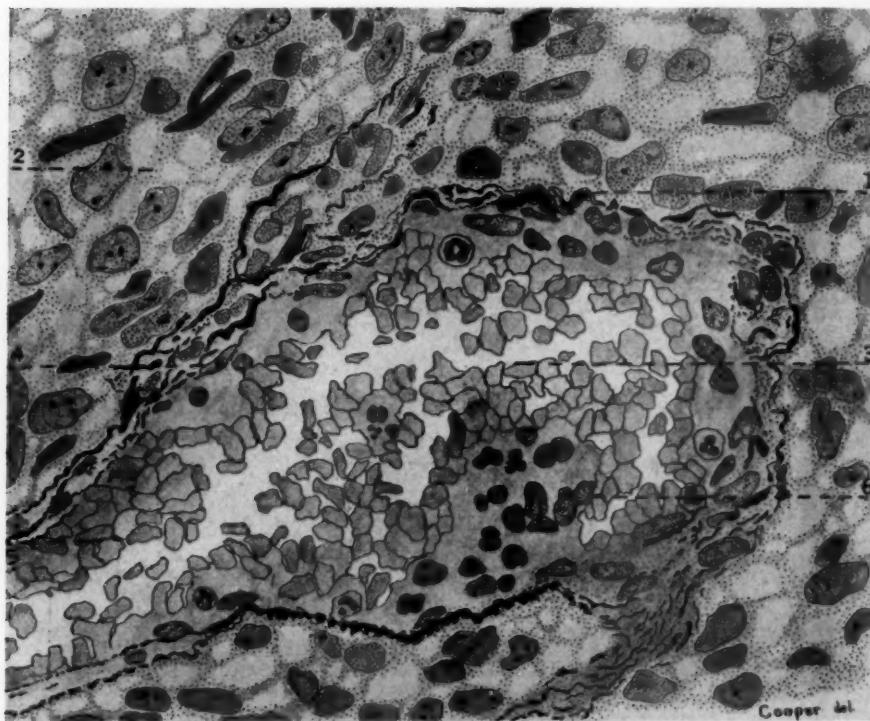


Fig. 3.—Camera lucida drawing of a portion of the section shown in figure 2 (adenocarcinoma of the lower lid [grade 3]). It shows the relation of reticular fibrils to capillary endothelium;  $\times 1,000$ . The numerals indicate (1) reticulum, (2) tumor, (3) capillary, (4) capillary endothelium, (5) erythrocytes and (6) leukocytes.

newly deposited collagen fibers; (3) stroma composed of densely packed collagenous fibers, as found for example, in scirrhouous carcinoma.

There is an apparent parallelism between the type of stroma and the reticulum content of the tumors. The areolar stroma is rich in reticulum, which appears as a fine, interlacing network of fibrils throughout the entire substance of the stroma. Tumors in which this

type of stroma is scanty naturally contain relatively small quantities of reticulum (fig. 2). Those which contain abundant stroma of this sort are rich in reticulum (fig. 4). Where the stroma is composed of young connective tissue fibers, the reticulum is usually present in abundance; where it is made up of densely packed collagenous connective tissue, reticulum is, as a rule, scanty or absent. This difference is illustrated by a section of an adenocarcinoma of the breast (fig. 5), which shows areas of growing epithelium, separated by wide bands of dense fibrous tissue and fat, such as would normally be found in breast tissue. Where normal acini remained, a basement lining of reticulum was

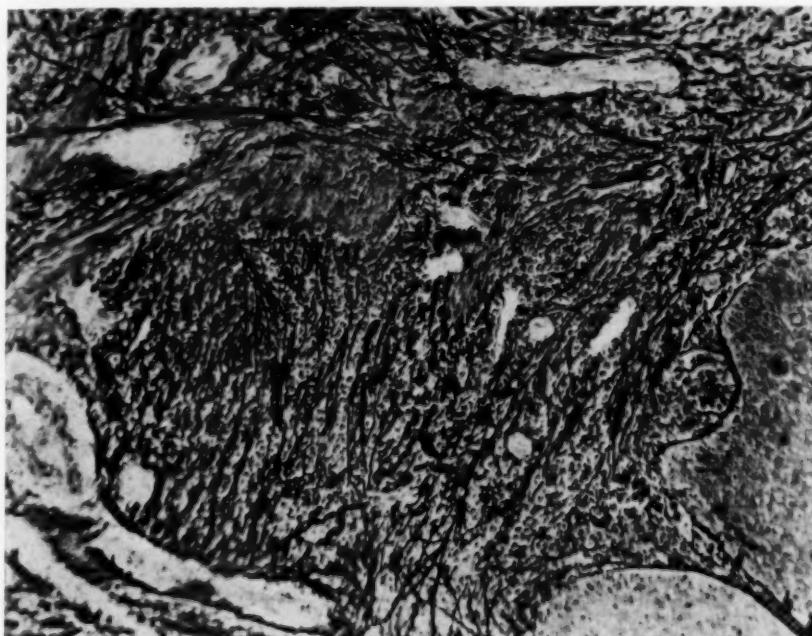


Fig. 4.—Colloid carcinoma of the rectum (grade 2), showing abundance of reticulum in the stroma of a tumor containing considerable quantities of stroma;  $\times 125$ .

present. Each cancer nest was encircled by reticulum. Lymphocytic infiltrations were present in the areas of new growth, and the stroma in this region was abundant in fibroblasts, with the connective tissue fibers loosely arranged. In this young, growing fibroblastic tissue, a fine network of reticulum was present. A short distance away, in the dense, old fibrous masses, no reticulum was present. This picture was repeated in each area of cancer cells observed, thus furnishing an instance of a specimen showing abundant reticulum in the vicinity of growing connective tissue, in contrast with little reticulum in the dense

stroma. Finally, there is a type of scirrhous cancer consisting of a few epithelial nests in dense fibrous stroma, in which virtually no reticulum is to be observed. There are varying gradations between the types described, but the impression is gained that the distribution of reticulum in cancer depends distinctly on the character of the stroma. It has been shown experimentally by Maximow<sup>8</sup> and McKinney<sup>9</sup> that reticulum is probably an early form of connective tissue, precollagenous in character. This affords an explanation for its presence in early growing stroma and its absence in consolidated stroma and scar tissue.

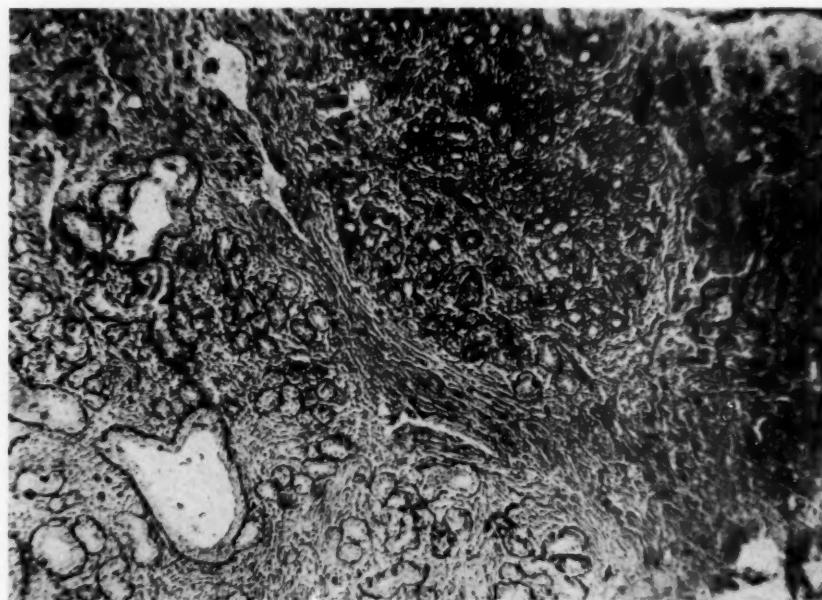


Fig. 5.—Adenocarcinoma of the breast (grade 4), showing islands of tubules separated by wide bands of connective tissue. Reticulum is relatively scant in the dense fibrous tissue, but abundant in the loose stroma in the vicinity of growing tubules.

In respect to the relationship between reticulum and the character of the stroma, it may be said that when the stroma is loose, areolar or fibroblastic in type, or indicative of the presence of young, growing connective tissue, it is rich in reticulum. If such stroma is abundant in a tumor, the reticulum in the tumor as a whole is abundant. If such stroma is not present in any considerable quantity, even though it is rich in reticulum, the quantity of reticulum in the tumor as a whole may be very small. Tumors which contain dense collagenous stroma contain little reticulum.

Reticulum appears to be concentrated at the periphery of the parenchymatous masses, whether they are in the form of epithelial cell nests or in that of acini or tubules. This relationship of reticulum to parenchyma may be illustrated by describing a section of a squamous cell carcinoma of the cervix (fig. 2). The histologic arrangement is one of large masses of epithelium, the centers of most of them tending to pearl formation. The nests are close together and appear to form practically the sole structure of the tumor, except for the presence of an occasional lymphocyte and capillary. Such a section under high magnification shows a double black line between contiguous nests of epithelium, each line applied to the periphery of a nest, and, when a capillary happens to lie between these nests, these two lines apply themselves to the periphery of the endothelium of the capillary, to form an encircling layer for it. The reticulum does not penetrate into the cell masses, but lies at the periphery of the epithelium. Occasionally, however, the reticulum penetrates the outer layer of cells of the epithelial nests, and the presence of a limiting membrane of reticulum about parenchymatous cells is not always noted; where the cancer grows very rapidly, in the form of sheets and isolated cells, the peripheral layer of reticulum is absent. Reticulum is not always found circumscribing pearls of squamous cell carcinomas that are completely keratinized. However, if a rim of viable epithelial cells remains, a circumscribing layer of reticulum may be present. Several such contrasting arrangements were observed lying side by side in the same section.

We have already referred to Rinehart's work<sup>15</sup> demonstrating the widespread abundance of reticulum in all tissues and its relationship to the capillary bed and to glandular structures. The relationship to parenchyma is established in the embryo by an ingrowth of epithelium into the mesenchyme, the precursor of reticulum applying itself to the periphery of the epithelial tongue, as a basement membrane. A similar process in growing carcinoma explains the presence of reticulum at the periphery of cancer nests. Where cancer growth is not too rapid, and the epithelium pushes into the stroma as cords, nests and tubules, the reticulum is pushed forward and concentrated, as it were, at the stroma-epithelial junction. The reticulum does not penetrate into the cell masses, except on rare occasions when it may lie between the cells of the outer layer. In such instances, as also in the case in which the epithelial growth is rapid and in sheet formation, the reticulum is not wholly pushed forward, but, instead, the cells may grow between the reticular fibers.

The accompanying table furnishes a survey of the fifty-six tumors examined, so arranged as to furnish a view of the grades of the tumors correlated with the quantities of reticulum. In this table, it is readily seen that there is no apparent parallelism between the grade of differentiation of a tumor and the amount of reticulum present. If we represent the absence of reticulum by the figure 0, and if we represent its presence quantitatively by the figures 1 to 4, then it is apparent from the table that the tumors of each grade fall rather evenly into two classes: those with no reticulum or very little (groups 0 and 1) and those with a moderate or considerable amount of reticulum (groups 2, 3 and 4). Of the six tumors of grade 1, four belong to groups 0 and 1, while two belong to groups 2 and 3. Fourteen of the thirty tumors of grade 2 are in groups 0 and 1; the remaining sixteen are in groups 2, 3 and 4. Of the eighteen tumors of grade 3, nine fall into groups 0 and 1, while the remaining nine fall into groups 2, 3 and 4.

*Relation of Grade of Tumor to Quantity of Reticulum*

Number of Tumors	Grade	Quantity of Reticulum				
		0	1	2	3	4
6.....	1	2	2	1	1	0
30.....	2	3	11	2	7	7
18.....	3	7	2	4	3	2
2.....	4	0	0	1	0	1

There are two tumors of grade 4; one contains little reticulum; the other contains much. Only the fifty-six tumors which were graded during their routine pathologic examination are included in this table.

Summarizing our observations concerning the relationship between reticulum content and malignancy of tumors, we may state that the degree of differentiation of malignancy, as expressed by grading, is dependent on characteristics of the epithelial cells; reticulum is a part of the stroma, and the effect of epithelial differentiation on the growth of reticulum is no greater than its stimulating effect on the new growth of stroma.

#### CONCLUSIONS

The distribution of reticulum in cancer does not depend on the degree of differentiation of the tumor. It depends on the character of the stroma of the tumor, being abundant when the stroma is made up largely of areolar or of young, growing connective tissue, and scanty when the stroma is made up largely of dense fibrous tissue. The amount of reticulum in a tumor depends also on the type of tissue in which the tumor is growing. Reticulum is abundant if the tissue in which the tumor is growing contains, normally, a large amount of reticulum.

## SHOCK SYNDROME IN MERCURIC CHLORIDE POISONING

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When death results from mercuric chloride within forty-eight hours, it frequently presents features resembling traumatic shock. There is progressive decline in blood pressure; the pulse becomes rapid and weak; respirations become rapid and shallow; the temperature may be subnormal and the skin pale and clammy.

Formerly most cases of circulatory failure were attributed to deficiency in cardiac function even though the hearts in such cases showed no pathologic conditions and there was no other evident reason for cardiac failure. Recently it has been shown that circulatory failure may result from other than cardiac or vasomotor causes. Surgical or traumatic shock is essentially a condition of circulatory failure, yet in shock produced experimentally it has been shown that the failure is not cardiac in origin. The heart in such experiments is able to maintain blood pressure at normal or even higher levels if it is provided with fluid and with adequate peripheral resistance. Nor is the vasomotor mechanism defective; during shock the peripheral arteries are found contracted almost to the obliteration of their lumens. There is strong evidence that the circulatory failure in shock is due to capillary dilatation; that loss of effective blood volume results when in extensive areas the capillaries become dilated and engorged; and that the circulation is defective because of inadequate return of blood to the heart. Cannon applied the term *exemia* to this condition. Capillary dilatation should be included among the causes for circulatory failure.

Moon and Kennedy<sup>1</sup> called attention to gross and microscopic tissue changes in traumatic shock. They believe these changes represent the characteristic pathology of that condition. Postmortem examination in human cases and in shock produced experimentally in dogs showed widespread capillary dilatation and congestion, edema, especially of the lungs, and petechial hemorrhages in serous surfaces. These findings corroborate the explanation that shock is due to capillary damage, dilatation and permeability resulting from the action of injurious substances

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1. Moon, V. H., and Kennedy, P. J.: Arch. Path. 14:360, 1932.

carried by the blood. Dale and Richards<sup>2</sup> and Dale and Laidlaw<sup>3</sup> found that histamine would produce these effects if introduced into the blood. Krogh<sup>4</sup> showed that the same effects may be produced by a wide variety of substances classed as capillary poisons. Following the action of such agents, the tissue changes were identical with those observed by Moon and Kennedy in shock. The organs appeared to contain an abnormal quantity of blood. Bleedings from minute vessels were frequent. The intestinal mucosa was abnormally congested. Often there was blood-tinged fluid in the serous cavities. Microscopically, the capillaries and venules were markedly dilated, and there were edema and numerous capillary hemorrhages in the lungs, mucosae, liver and kidneys.

Since the changes described are the characteristic results of capillary injury, it will be important to determine whether these changes are present in other conditions in which circulatory failure is a prominent clinical feature. A case of mercuric chloride poisoning presented the clinical features of shock. Search was made for evidence indicating whether the circulatory failure resulted from cardiac deficiency or from injury to capillaries.

#### REPORT OF A CASE

A white man, aged 39, had swallowed 175 grains (11.3 Gm.) of mercuric chloride in tablet form. It was not learned whether water was taken also. He walked into the hospital about thirty minutes later (5:50 a. m.). There was no vomiting. He complained of a burning sensation in the throat and mouth. The tongue, pharynx and fossae were dry and raw and showed the local effect of the mercuric chloride. There was pain on swallowing. He was very cyanotic and cold, and the respirations were rapid. The radial pulse was barely perceptible. He was given gastric lavage with egg albumin and water. Immediate treatment for shock was instituted. Hot water bottles and blankets were applied. Caffeine and strychnine were given. The patient reacted somewhat from shock.

He was given 1,000 cc. of saline solution intravenously three hours after admission. Further medical treatment included sodium thiosulphate, colonic irrigation, magnesium sulphate and pilocarpine. Atropine, strychnine and caffeine were given as stimulants. At 1 p. m., the pulse was not perceptible, nor could the blood pressure be taken. He was given dextrose and saline solution intravenously. The blood pressure rose to 82 systolic and 64 diastolic. There was no voiding of urine. The following morning he was rational. The pulse was rapid but not irregular. Dextrose solution and sodium thiosulphate were given intravenously. Colonic irrigation was repeated. He complained of pain on only two occasions. From 4 p. m. to 5 p. m. there was frequent vomiting of bloody material. The abdomen became very distended and tympanitic. The temperature, which was subnormal on admission, rose to 102 F. shortly before death. He died at 7 p. m., thirty-seven hours after admission.

Note by Dr. E. Quin Thornton: "This male adult who ingested about 175 grains of mercury bichloride in the form of tablets, came to us within an hour afterward.

2. Dale, H. H., and Richards, A. N.: *J. Physiol.* **52**:110, 1918.

3. Dale, H. H., and Laidlaw, P. P.: *J. Physiol.* **52**:355, 1919.

4. Krogh, A.: *Anatomy and Physiology of Capillaries*, revised ed., New Haven, Conn., Yale University Press, 1930, p. 197.

His most pronounced signs and symptoms were those of mental confusion and profound shock. There was no evidence of heart block nor of disturbance of the contraction impulse. He did not show marked gastro-intestinal symptoms. He neither purged nor vomited severely and was comparatively free from abdominal pain. There was marked excoriation of the mouth and tongue. During 37 hours in the hospital he voided only once, which was within two hours after admission. This was involuntary, so no specimen of urine was obtained. He had neither convulsions nor paralysis. From profound shock he went gradually into coma and died a few hours later."

*Autopsy.*—The body was that of a young white man, well developed and well nourished. There was a discoloration of the lips, but no ulceration. The mouth could not be examined because of postmortem rigidity. The abdomen was distended, and there was marked postmortem rigidity. No bruises or injuries were present. There was no evidence of subcutaneous edema. The subcutaneous and omental fat was moderate in quantity. The entire visceral peritoneum had a deep dull rose color. The superficial vessels were distended. The entire bowel was relaxed and distended. There was about 500 cc. of blood-tinged fluid in the peritoneal cavity. This had a wine-red color due to hemolysis of blood.

The pericardium contained about 25 cc. of blood-tinged fluid but showed no adhesions. Each pleural cavity contained about 500 cc. of blood-tinged fluid, and each cavity was interrupted by a few dense adhesions about the apex.

The heart weighed 300 Gm. and measured 14 by 8 by 5 cm. The superficial vessels were congested, and the cardiac muscle was dull red but contracted, and the cavities were of normal size. There was no lesion of the endocardium or of the valve leaflets. The blood was partially hemolyzed, and the endocardium was stained red. The myocardium was not more friable than normal. There was no evidence of dilatation.

The left lung weighed 880 Gm. It was very heavy, but not consolidated. It had a deep purplish-red color throughout. The lung was also engorged with blood, and the surfaces made by sectioning exuded quantities of bloody, frothy fluid. Near the apex of the left lung there were a few small firm fibrous areas and scars. These areas were contracted and fibrotic. There was no evidence of consolidation. The right lung weighed 950 Gm. It also was engorged and contained large amounts of bloody, frothy fluid. In other respects it resembled the left lung. The pleurae contained numerous petechiae.

The spleen weighed 260 Gm. It was deep red and rather soft. The cut surface was deep red, and the tissue was friable. The lymphoid follicles were not distinctly seen.

The left kidney weighed 150 Gm. The capsule stripped readily, leaving a smooth, pale surface. On section, the cortex was slightly thicker than normal and had a pale, whitish appearance in sharp contrast to the congested, red medulla. The cut surface of the cortex had a lusterless, dry, opaque appearance. The pelvis of the kidney appeared normal. The right kidney weighed 150 Gm. It presented the same features as the left kidney.

In the lower portion of the esophagus, the lining was eroded and seemed ulcerated. The mucosa of the stomach was dull red, and there were numerous small whitish foci scattered throughout. The mucosa was not ulcerated. In the upper portion of the small intestine, including the duodenum and part of the jejunum, the mucous membrane was very deep red, ulcerated and apparently necrotic. The lower portion of the small intestine and the colon appeared normal, except for the dull red color of the mucosa.

The liver weighed 1,460 Gm. Its surfaces were smooth and its color normal. The substance of the liver was soft, and on section it had a peculiar yellowish, mottled appearance.

The gallbladder was distended with dark green bile. The duct was patulous.

The pancreas appeared normal. The suprarenal glands appeared normal. The ureters were normal. The bladder contained about 20 cc. of urine. The wall of the bladder appeared normal. There was no enlargement of the lymph nodes. The great vessels disclosed no changes. No evidence of sclerosis was observed.

The outstanding postmortem features were the marked congestion and edema of the viscera, particularly of the pulmonary and gastro-



Fig. 1.—Gross photograph of lungs from a person who died of mercuric chloride poisoning. A lung of normal color (middle) was photographed for comparison.

intestinal tracts, the presence of blood-tinged fluid in the serous cavities, the presence of capillary hemorrhages and the usual effects of mercuric chloride on the gastro-intestinal mucosae, the liver and the kidneys. The increased weight of the lungs is particularly significant. These were markedly edematous and engorged (fig. 1). Their combined weight was 1,830 Gm. after much fluid had escaped following section and pressure on several of the lobes. An increase of about 1,500 Gm. above the normal weight was apparently due to blood and fluid. This indicates both the nature and the gravity of the circulatory disturbance.

*Histologic Examination.*—Kidneys: These showed complete necrosis of all portions of the tubules; relatively unchanged glomeruli, with moderate congestion of some and moderate edema of others; engorgement of the capillaries of the

medulla, and moderate edema of the medullary interstitial tissue. Some of the collecting tubules contained desquamated cells.

**Lungs:** Sections from various portions of the lung showed widespread extreme capillary dilatation, dilatation of venules and numerous areas of capillary hemorrhage. There was marked edema; many of the alveoli were completely filled and others partially filled with fluid, which appeared to contain much albumin. There were no areas of cellular infiltration indicating infection. The edema and congestion were more extreme in the posterior portions, but were very marked in the lateral and anterior portions of the lobes (fig. 2). A few well encapsulated areas of tuberculous infection were present in the apices.

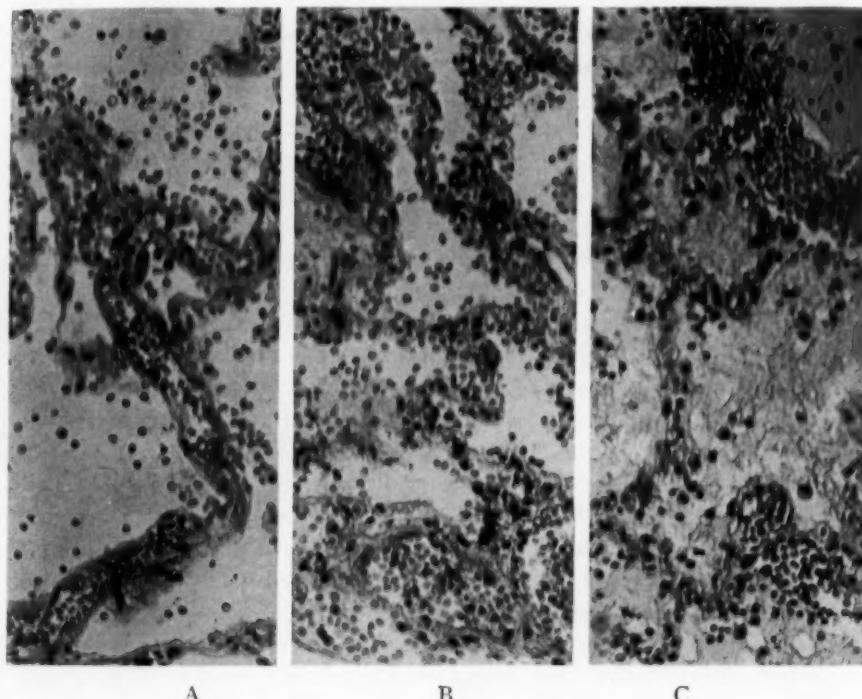


Fig. 2.—Photomicrographs of lung in a case of mercuric chloride poisoning: *A*, anterior margin; *B*, lateral, and *C*, posterior portion. Small extravasations and marked engorgement of capillaries and venules are present in all portions. Edema is most marked in the posterior portion.

**Heart:** There was no evidence of degeneration of the fibers of the myocardium. The capillaries and venules were slightly congested.

**Liver:** The cytoplasm of the liver cells was not homogeneous. It contained vacuoles, granules and an irregularly stained reticulum. In many areas the cells were smaller than normal; in others they were of normal size. These changes were most marked in the central zones. There was an excess of golden-brown pigment within the liver cells.

**Stomach:** The superficial portion of the mucosa showed marked postmortem autolysis. It is uncertain whether antemortem necrosis was present. The venules of the subserous and submucous layers were more distended than normally. No other changes were noted.

Ileum: The postmortem changes of the mucosa were very marked. There was more extensive vascular dilatation in the wall of the ileum than in the stomach. Moderate edema was also present.

The outstanding histologic features were necrosis of the tubular epithelium, acute degeneration of the liver and widespread capillary congestion, capillary hemorrhages and edema especially of the lungs. Capillary damage resulting in increased permeability was evident. The renal necrosis and hepatic degeneration are characteristic of mercuric poisoning. Circulatory changes such as those found here have not been considered as characteristic of mercuric poisoning, but they coincide accurately with the pathologic conditions observed in shock.

The chambers of the heart were not dilated. The valvular orifices were of normal size. The valves showed no defects, and the myocardium was firm and of normal color. The heart showed no changes of any kind which would make cardiac failure seem probable.

McNider<sup>5</sup> produced acute poisoning by injecting 1 per cent mercuric chloride solution intravenously. Doses equivalent to 15 mg. per kilogram of body weight caused eight dogs to die within forty-eight hours. The details of postmortem examinations were not given. McNider stated that the condition of these animals before death was that of shock or collapse. This he interpreted as a disturbance of the functioning capacity of the vascular mechanism, induced by deflection of blood to the splanchnic viscera. This mechanism was an acceptable explanation of shock at the time his experiments were made (1918). He stated that the dogs in this group did not die of renal insufficiency.

Goldblatt<sup>6</sup> analyzed nineteen proved cases and nineteen suspected cases of mercuric chloride poisoning. In nine of the proved cases, a blood pressure of 100 mm. or less was recorded. In three the blood pressure was not taken. He noted that a progressive decline in blood pressure was one of the immediate signs of acute mercuric poisoning. This was accompanied by dyspnea, air hunger, increased respiratory rate and cold body surfaces as the intoxication approached a fatal termination. Goldblatt also studied the effects of mercuric chloride poisoning in dogs. "When death occurred immediately following administration of mercuric chloride by mouth or by vein, intense edema of the lungs was the most characteristic finding." Marked congestion of the lungs and occasionally very marked subpleural hemorrhages were also noted.

Congestion and edema of the lungs were noted by Harmon<sup>7</sup> in postmortem examinations of persons to whom poisonous doses of mercuric chloride had been given intravenously.

5. McNider, W. DeB.: *J. Exper. Med.* **27**:519, 1918.

6. Goldblatt, S.: *Am. J. M. Sc.* **176**:645, 1928; *J. Lab. & Clin. Med.* **14**:145, 1928.

7. Harmon, E. L.: *Am. J. Path.* **4**:321, 1928.

Other authors have made similar incidental observations, but made no comments on the relationship between the visible circulatory changes and the shocklike clinical manifestations.

Occasionally mercuric chloride causes immediate death by disturbance of the conductivity of the heart muscle.<sup>8</sup> Arrhythmia and other evidences of heart block, rather than of shock, are the prominent manifestations in such cases. The case here reported showed no clinical evidence of interrupted conductivity.

Landis,<sup>9</sup> using the micro-injection technic, studied in living capillaries the effects of various agents injected into the blood. He found that injection of such agents as 10 per cent alcohol or 1:10,000 mercuric chloride solution caused injury to capillary walls similar to that caused by ethyl carbamate (urethane). They markedly increased capillary permeability. Capillaries treated with mercuric chloride were seven times more permeable than normal capillaries. Evidently mercuric chloride may produce capillary damage similar to that caused by other capillary poisons described by Krogh.<sup>4</sup> Heubner<sup>10</sup> divided into subgroups the substances which affect capillaries: those like ethyl-morphine hydrochloride the sole effect of which is on capillaries; those like histamine which may act on capillaries and nerves, and those like arsenic which may act on capillaries and tissue cells. Because of its characteristic effect on the cells of the kidney and liver, mercuric chloride belongs in the latter subgroup of capillary poisons.

#### SUMMARY

A man with mercuric chloride poisoning died of circulatory failure within thirty-seven hours. There was no clinical evidence of disturbance of the cardiac contraction impulse. There was no cardiac lesion which would indicate defective cardiac function as a cause of the circulatory failure.

The shock syndrome was the most prominent clinical manifestation.

Postmortem examination showed both gross and microscopic changes characteristic of shock: widespread dilatation of capillaries and venules, with edema and capillary hemorrhages. These were most marked in the organs of respiration.

The evidence indicates that mercuric chloride may act as a capillary poison; that as such it produces the same circulatory phenomena and the same gross and microscopic changes as are found in shock.

8. McCrea, F. D., and Meek, W. J.: *J. Pharmacol. & Exper. Therap.* **36**:295, 1929.

9. Landis, E. M.: *Am. J. Physiol.* **82**:217, 1927.

10. Heubner, W.: *Arch. f. exper. Path. u. Pharmakol.* **107**:129, 1925.

## COCCIDIOSIS OF THE LIVER IN RABBITS

### III. EXPERIMENTAL STUDY OF THE HISTOGENESIS OF COCCIDIOSIS OF THE LIVER

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#### SCHIZOGONY

It seemed desirable, for several reasons, to study the earliest lesions of coccidiosis of the liver and especially to find out where the earliest lesions can be found and how long it takes after oral infection for these lesions to develop in the liver.

Two series of healthy 3 week old rabbits, litter mates, were used. These baby rabbits were kept in separate cages for several days before the experiment, and daily examinations of their feces for *Eimeria stiedae* were made by the flotation method;<sup>1</sup> only litter mates free from oocysts of *Eimeria stiedae* were used. All animals except one, which was kept as a control, were infected with sporulated oocysts of *Eimeria stiedae* by mouth or by stomach tube, and each day one animal was put to death.

In addition to these two series, many other rabbits which had been infected at a known date were examined.

All the animals were infected with from 6 to 10 cc. of a suspension of oocysts in an equal volume of saline solution, as this dose proved to be sufficient ordinarily to insure infection.

The data on the length of time required for the appearance of the earliest demonstrable lesions in the liver are given in table 1. From these data it can be seen that early stages of coccidiosis of the liver were found in from 6 to 10 days after infection. Very likely, lesions were present in the livers before this time, but being rare were difficult to detect without the aid of serial sections. Although the number of sporozoites reaching the liver may have been of importance, especially so far as the primary multiplicity of the lesions was concerned, the actual extent of the disease depended chiefly on the process of schizogony, by which the infection was propagated throughout the liver.

It has to be borne in mind that not all sporozoites of oocysts fed at one time were liberated at the same time; most of the oocysts were retained in the stomach for some time and were only gradually allowed to escape into the duodenum. This was easily demonstrated by inspecting the gastric contents of the infected animals

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1. Hegner and Andrews: Problems and Methods of Research in Protozoology, New York, The Macmillan Company, 1930.

on successive days after the administration of the oocysts. As more and more sporozoites were liberated in the duodenum, some of them eventually succeeded in reaching the liver at different intervals of time. This may account for slight irregularities in the time of appearance and the intensity of the lesions appearing in the livers of animals which had been infected simultaneously.

In the very early stages of the infection, the livers on gross examination appeared normal. Soon, however, small white specks and delicate white streaks could be seen through Glisson's capsule; these represented the enlarged bile ducts and the cellular infiltrations around them.

TABLE 1.—*Time of Appearance of Lesions in the Liver After Infection by Mouth with Oocysts of Eimeria Stiedae*

Animal	Age, Weeks	Findings in Liver at Autopsy	Oocysts in Bile of Gallbladder at Autopsy	Duration of Experiment, Days	Result
<b>Series 1</b>					
1	3	No evidence of coccidiosis	0	1	0
2	3	No evidence of coccidiosis	0	2	0
3	3	No evidence of coccidiosis	0	3	0
4	3	No evidence of coccidiosis	0	4	0
5	3	No evidence of coccidiosis	0	5	0
6	3	Early coccidiosis, schizogony	0	7	+
7	3	No evidence of coccidiosis	0	7	Control
<b>Series 2</b>					
1	3	No evidence of coccidiosis	0	1	0
2	3	No evidence of coccidiosis	0	2	0
3	3	No evidence of coccidiosis	0	3	0
4	3	No evidence of coccidiosis	0	3	0
5	3	No evidence of coccidiosis	0	4	0
6	3	No evidence of coccidiosis	0	5	0
7	3	No evidence of coccidiosis	0	5	0
8	3	Early coccidiosis, schizogony	0	7	+
9	3	Early coccidiosis, schizogony	0	8	+
10	3	No evidence of coccidiosis	0	8	Control
<b>Miscellaneous</b>					
1	4	No evidence of coccidiosis	0	6	0
2	4	Early coccidiosis, schizogony	0	6	+
3	4	Early coccidiosis, schizogony	0	7	+
4	Adult	Early coccidiosis, schizogony	0	8	+
5	Adult	Early coccidiosis, schizogony	0	10	+

Since it is not known how long it takes sporozoites or schizonts to go through the cycle of schizogony and cause infection of neighboring epithelial cells, the duration of the early lesions could be only approximately estimated by the extent of the microscopic lesion present at a certain day after the infection. The number of merozoites formed in the epithelial cells after the penetration of the sporozoites is not exactly known; it varies according to different authors. Reich<sup>2</sup> reported that the asexual multiplication results in the formation of sixteen merozoites, while in the experience of Wenyon<sup>3</sup> up to thirty or more can be found; von Wasielewski<sup>4</sup> saw as many as one hundred merozoites in one cell.

2. Reich: Arch. f. Protistenk. **28**:1, 1912.

3. Wenyon, C. M.: Protozoology, New York, William Wood & Company, 1926.

4. von Wasielewski: Studien und Mikrophotogramme zur Kenntnis der pathogenen Protozoen, Leipzig, J. A. Barth, 1904.

In my series the earliest evidence of coccidiosis of the liver was observed six days after infection. Grossly, the liver appeared unchanged, but sections of this organ revealed interesting and instructive pictures.

The periportal fields were very prominent and were infiltrated by a variety of cells, eosinophils, lymphocytes, plasma cells, large monocytes and an occasional neutrophilic leukocyte. The epithelial cells of the small bile ducts and bile pre-capillaries were markedly swollen, whereby the lumens of these ducts became greatly narrowed. There was marked proliferation of the biliary epithelium, and mitotic figures could often be seen. A few of the epithelial cells of the small bile ducts contained curled up sporozoites, which, in rare instances, were undergoing schizogony. The sporozoites were found within vacuoles in the epithelial cells, varying in position from near the basal membrane to closer to the lumen of the duct (fig. 1 A). The proliferation of the epithelial cells was indeed not limited to bile ducts showing sporozoites in their cells, but was present in many ducts that showed no sporozoites in their epithelium. Likewise, the infiltrations of the periportal fields were not limited to those in which the bile ducts were infected, but were commonly seen throughout the sections, giving the impression that the reaction was out of proportion to the extent of the infection. A thorough microscopic examination of several slides of this liver failed to show free sporozoites in the lumens of bile ducts or in the blood and lymph vessels. In the tissues of the periportal fields, however, occasional round or oblong bodies were encountered which resembled sporozoites so far as size, shape and structural characteristics were concerned. One of these bodies was seen within a vacuole close to the basement membrane just outside of a small bile duct (fig. 1 B). In view of the results of the experiments reported in a previous paper,<sup>5</sup> this finding was of significance and will be discussed later.

According to some authors (Seifried<sup>6</sup>), the sporozoites infect the distal portion of the common bile duct first, and from there the infection spreads by means of merozoites causing "contact infection" of neighboring cells until the intrahepatic bile ducts are reached. In order to test this hypothesis, the distal portion of the common bile duct was examined in all cases. In no case could infection of the common bile duct be demonstrated prior to the infection of the intrahepatic bile ducts. On the contrary, during the very early stages of schizogony in the intrahepatic bile ducts, no evidence of infection of the epithelial cells of the common bile duct could be demonstrated; only slight infection of the ductus choledochus was present in cases in which the process of schizogony in the intrahepatic bile ducts was pronounced, and up to advanced stages of schizogony the lesions in the common bile duct lagged in intensity distinctly behind those of the intrahepatic bile ducts.

For instance, in the two series of rabbit litters (table 1), no evidence of coccidiosis of the intrahepatic bile ducts or of the common bile duct was found in animals 1 to 5 of series 1 and animals 1 to 7 of series 2; animal 6 of series 1

5. Smetana: Coccidiosis of the Liver in Rabbits: II. Experimental Study of the Mode of Infection of the Liver, *Arch. Path.* **15**:330, 1933.

6. Seifried: *Ergebn. d. allg. Path. u. path. Anat.* **22**:513, 1927.

and animal 8 of series 2 showed early infection of the intrahepatic bile ducts, but no evidence of infection of the common bile duct; rabbit 9 of series 2 had advanced lesions in the stage of schizogony in the intrahepatic bile ducts, but very early, scanty lesions in some of the epithelial cells of the distal portion of the common

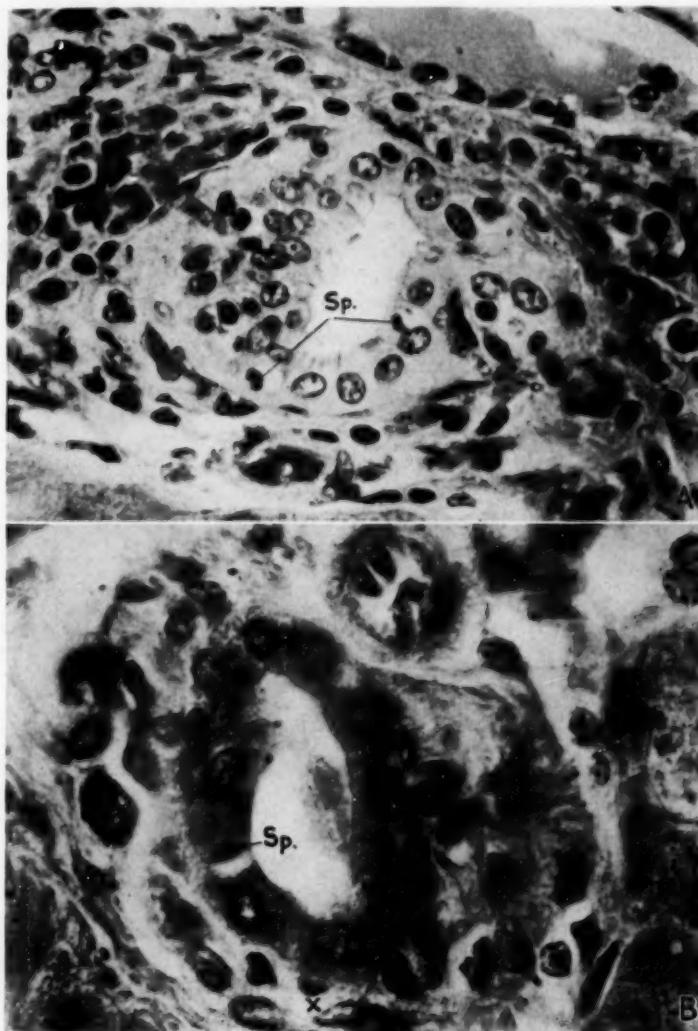


Fig. 1.—Liver of rabbit 2871 six days after infection. *A*, portal field infiltrated by lymphocytes, plasma cells and eosinophils;  $\times 720$ . Note the marked proliferation of the biliary epithelium. *Sp.* indicates sporozoites in epithelial cells of the bile ducts. *B*, a bile duct; (oil immersion;  $\times 1050$ ). *X* indicates a sporozoite outside the bile duct. Note the enlargement of the nucleus of the epithelial cell next to this sporozoite.

bile duct. Six days after infection, animal 2 of the miscellaneous group showed very early lesions in the liver, but none in the common bile duct. There were a few infected epithelial cells in the common bile duct of animal 3 of this group seven days after feeding, while the changes in the intrahepatic bile ducts were advanced. Both common bile duct and intrahepatic bile ducts were markedly affected in rabbit 2 (table 2) eleven days after infection by mouth.

All stages of development of schizonts could be studied in the section of one bile duct, from a single sporozoite or merozoite, its division, up to the formation of a multitude of pointed bodies held together like staves of a barrel, until the schizonts finally escaped from the fragments of the epithelial cells within which they had matured. In advanced stages of schizogony, free merozoites within the lumens of the bile ducts, as well as merozoites penetrating into the epithelial cells of bile ducts, could easily be found. The newly liberated merozoites quickly occupied available uninfected epithelial cells, so that a saturation point would seem to have been reached if it had not been for the reaction of the biliary epithelium: the great demand of epithelial cells of the bile ducts, most of which were

TABLE 2.—*Appearance of Gametogony*

Animal	Duration of Experiment, Days	Findings at Autopsy	Gametogony
1	10	Schizogony advanced, no gametogony.....	0
2	11	Schizogony advanced, no gametogony.....	0
3	11	Schizogony advanced, early gametogony.....	+
4	12	Schizogony advanced, early gametogony.....	++?
5	12	Schizogony advanced, no gametogony.....	0
6	13	Schizogony advanced, early gametogony.....	+
7	13	Schizogony advanced, early gametogony.....	+
8	14	Schizogony advanced, early gametogony.....	+
9	14	Schizogony advanced, early gametogony.....	+
10	15	Schizogony advanced, moderate gametogony.....	++
11	18	Little schizogony, gametogony advanced.....	+++

undoubtedly severely damaged by the organisms, led to a tremendous regeneration and proliferation of the biliary epithelium, resulting in the formation of high papillary folds lined with several layers of cells, most of which were inhabited by parasites.

#### GAMETOGONY

It was difficult to determine exactly the beginning of gametogony, because of the similarity of merozoites developing either into schizonts or into gametocytes; later stages of gametogony and mature gametocytes could, of course, be easily identified. The change from schizogony to gametogony was gradual, and there seemed to be some variation in the time of the appearance of the gametocytes, not only in different animals, but also in different parts of the biliary system of the same animal.

The times of appearance of gametogony in a series of animals, covering a range of from ten to eighteen days after oral infection, are given in table 2.

Definite evidence of the presence of gametocytes was seen about two weeks after infection. Before that time one might find an occasional sexual form while schizogony was still predominant. After the four-

teenth day of infection, gametogony became quite prominent and replaced schizogony more and more.

From about the fourteenth to the eighteenth day, both processes could be found in neighboring epithelial cells of the same bile duct, although it was perhaps more common to see schizogony in some of the bile ducts and gametogony in others. Three weeks after infection, practically only gametogony was present, and by this time many mature oocysts, either still attached to cells or liberated within the lumens of bile ducts, had developed.

Grossly, this stage was characterized by the presence of whitish nodules on the surface of the liver. The nodules varied in size from several millimeters up to a centimeter or more, and projected slightly over the surface of the liver. Their consistence varied; it was frequently soft and cystlike. On cut surface, these nodules contained a yellowish-white, puslike material which, on microscopic examination, was found to be almost entirely composed of liberated oocysts. The bile ducts at this stage were greatly dilated and tortuous; their lumens contained multitudes of oocysts. In addition, the common bile duct, usually a very delicate structure measuring about 1 mm. in diameter, became large and tortuous; its caliber was very wide, measuring up to about 0.5 cm., and its lumen was filled with oocysts.

The microscopic picture of the liver at this stage was that usually presented in textbooks and was very characteristic: The bile ducts were tremendously enlarged; their epithelial lining was thrown up into high folds similar to those seen in a papilloma. Practically all the cells contained macrogametocytes or microgametocytes and maturing oocysts, and the lumens of the ducts were filled with liberated oocysts. The large ducts were surrounded by a capsule partly representing the preformed connective tissue of the periportal fields, remnants of the supporting tissue of compressed and collapsed hepatic tissue of the vicinity and partly also newly formed fibrous tissue. In this capsule one often saw proliferating small bile ducts in which the epithelial cells might or might not be infested by parasites. Cellular infiltrations of varying intensity, composed of lymphocytes, plasma cells, eosinophils and occasional neutrophilic leukocytes, were scattered through the tissues of this capsule. The hepatic tissue surrounding the biliary channels was greatly reduced in amount and often showed atrophy due to the pressure of the expanded ducts. Commonly the normal structure of the liver was disturbed owing to the extension of connective tissue from one periportal field to another, whereby the lobule became completely surrounded by fibrous tissue containing proliferating small bile ducts or obstructed large bile ducts. However, the amount of connective tissue as well as the extent of the proliferation of small bile ducts varied in different cases; sometimes it was so insignificant that the large bile ducts almost bordered on more or less normal liver.

#### LATE STAGES OF COCCIDIOSIS OF THE LIVER

Most of the animals infected successfully with a large amount of oocysts of *Eimeria stiedae* succumbed in about from four to six weeks after infection. In these animals, the liver was tremendously enlarged and was studded with nodules of various sizes, while the parenchyma was reduced to narrow strips between the nodes. Jaundice almost always occurred, and the peritoneal cavity contained a varying amount of fluid. Generally the spleen was enlarged and firm.

Coccidiosis of the liver from natural infection is not necessarily fatal; on the contrary, the majority of rabbits survive a mild degree of infection. This fact can easily be proved by examination of the bile of the gallbladders of adult rabbits.<sup>5</sup> Many of the older animals harbor oocysts in the bile of the gallbladder without demonstrable lesions of the liver. More often, however, one finds old, encapsulated nodules, mostly containing degenerated oocysts which cannot be sporulated.

Some of the animals which had been successfully infected experimentally recovered. Study of the livers of these recovered animals revealed interesting facts concerning the regenerating power of bile ducts and hepatic tissue, and the results have an important bearing on the question of experimental cirrhosis of the liver in rabbits.

It was observed that after successful infection, proved by the presence of non-sporulated oocysts of *Eimeria stiedae* in the feces, some of the animals began to excrete oocysts that showed signs of degeneration and could no longer be sporulated. Besides the degenerated oocysts, only unfertilized oocysts were found in the feces of rabbits that had previously discharged normal fertilized oocysts, which had repeatedly been collected as material for infection. It was also noticed that such animals did not die at the expected time after infection, but recovered slowly.

The early stages of healing coccidiosis were difficult to recognize, as the microscopic picture at this time differed but slightly from that seen at the stage of advanced gametogony.

No schizogony could be demonstrated, and no merozoites were being formed; only gametocytes, in different stages of development, occupied the epithelial cells of the large bile ducts, and oocysts appeared in increasing numbers. The lesions at this stage represented the maximum extent of the infection, and because of the absence of schizonts and merozoites no new infection of cells could take place. Macrogametocytes and microgametocytes, however, continued their development until they reached maturity, when fertilization of macrogametes by microgametes could take place.

Other factors then entered into play which effectively checked any further advancement of the process. While up to this stage the biliary epithelium was mainly limited in rôle to the new formation of cells serving passively as hosts for schizonts and merozoites, it now took the lead in inhibiting further development and broke the way for removal of the parasites and restoration of the damaged structures.

The high papillary folds of many of the infected bile ducts disappeared owing to the disintegration of contaminated cells and the sloughing off of their supporting tissues. The bile ducts then represented large cavities, lined by a single layer of cuboidal or columnar epithelial cells, some of which still held oocysts or maturing gametocytes. The lumens usually contained many liberated oocysts and débris.

At one point, sometimes at several points of the inner lining of such a bile duct, there appeared peculiar cells which grew into the lumen and gradually filled it up completely. These cells varied greatly in size, and their outlines were indistinct, often forming a syncytium; not infrequently they formed multinucleated giant cells

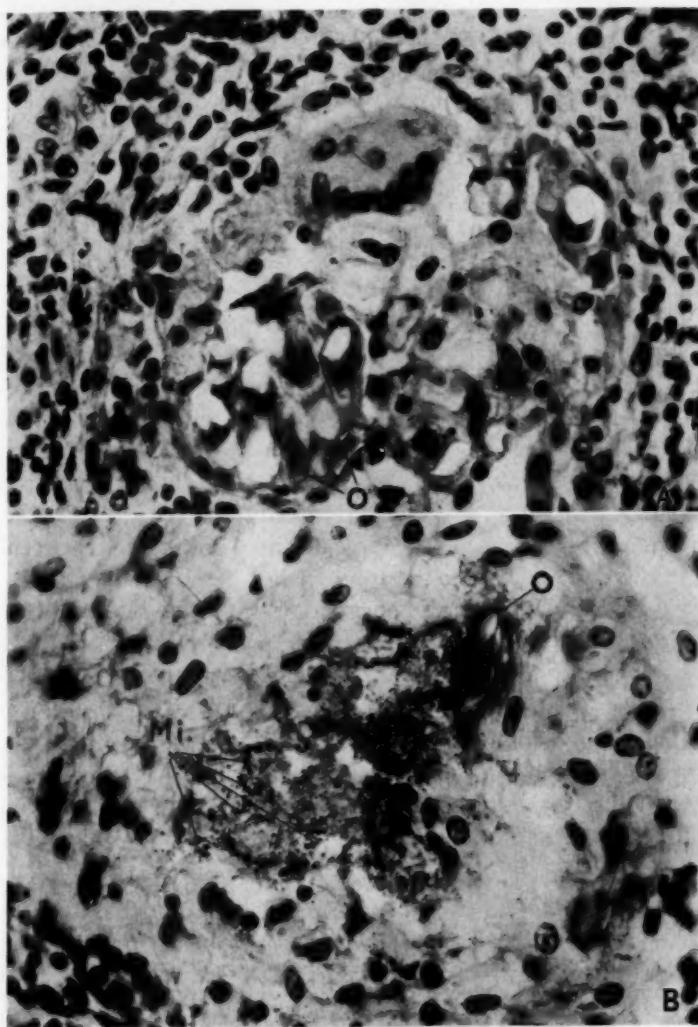


Fig. 2.—*A*, multinucleated giant cells surrounding distorted oocysts (*O*) within the lumen of a bile duct and, *B*, epithelial cells obliterating the lumen of a bile duct, twenty-seven days after infection of rabbit 572. In *B*, note distorted oocyst (*O*) and phagocytosed microgametes (*Mi*);  $\times 450$ .

(fig. 2 *A*). The cytoplasm was pale and sometimes foamy; the nuclei were vesicular in type, showing one or more nucleoli. Because of the proliferation of these cells, the oocysts and gametocytes still in the bile duct were surrounded, fixed in

place and partly destroyed. The effect on the microgametes was especially marked: their movements at first were restricted and later were completely suppressed, and the organisms were then phagocytosed by the cells (fig. 2B). The gametocytes, especially in the early stages of development, were soon destroyed and disappeared. Finally only oocysts remained impacted within and between the cells filling out the lumen of the bile duct. It was obvious that this attack on the parasites was very effective: the unprotected gametocytes apparently succumbed quickly; the microgametes could not move freely and were prevented from reaching available macrogametes, so that fertilization could no longer take place.

The obliteration of the lumen caused blockage of the entire distal portion and ramification of such a bile duct, which confined both the macrogametes and the microgametes, thus restricting the activity of the parasites in this portion of the biliary tract.

It was difficult to determine exactly the origin of the cells obliterating the lumens of the bile ducts. From studies of early stages of their appearance, however, it seemed most likely that these cells were modified epithelial cells of bile ducts: after the papilli of the ducts, holding the contaminated cells, had sloughed off, mitotic figures appeared in the remaining, rather flat, lining cells. Soon afterward groups of these peculiar cells were seen at one point or at several points of the lining and grew into the lumen, often completely filling it; their nuclei closely resembled those of the biliary epithelium (fig. 2). The basement membrane of larger ducts indicated the border line between these cells and the surrounding tissues; in smaller bile ducts having no basement membrane, the line of demarcation was indistinct. There was no evidence of granulation tissue within the lumens of bile ducts; on the contrary, the tissue plugging the lumens was characterized by the absence of capillaries and connective tissue cells. Only a few wandering cells, chiefly lymphocytes, could be seen.

At all stages of the infection, beginning with the early penetration of sporozoites into the epithelium of the biliary tract, the tissue surrounding the bile ducts showed signs of varying degrees of reaction. The periportal fields were greatly enlarged and encroached on the hepatic parenchyma. Neighboring fields often anastomosed and thus partly or completely surrounded a hepatic lobule. Cellular infiltrations were always present but varied in intensity. The periportal connective tissue was increased owing to condensation of the preformed stroma of the compressed and atrophied hepatic tissue as well as to new formation. Many newly formed bile ducts of precapillary type were encountered, especially in the later stages of gametogony, although there was great variation in the time of their appearance and in their number. In rare cases during gametogony there was such a marked increase of periportal connective tissue spreading from one field to another and containing numerous proliferating, newly formed bile ducts, that the picture resembled that of biliary cirrhosis (fig. 3). There was, however, no stasis of bile. The epithelial cells of the newly formed bile ducts were sometimes infected and sometimes not, depending on the stage of infection during which they were formed: During schizogony and early gametogony, the majority of them became infected; while in stages of exhaustion of gametogony, when practically only maturing gametocytes were present, no parasites were found in their epithelial cells.

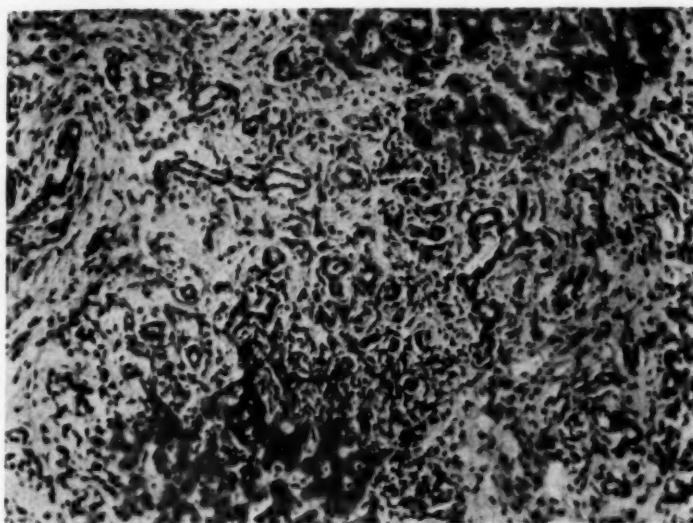


Fig. 3.—Liver of rabbit 4C eighteen days after infection;  $\times 100$ . Note scarring of liver and proliferation of small bile ducts, with separation of lobules of the liver by scar tissue.

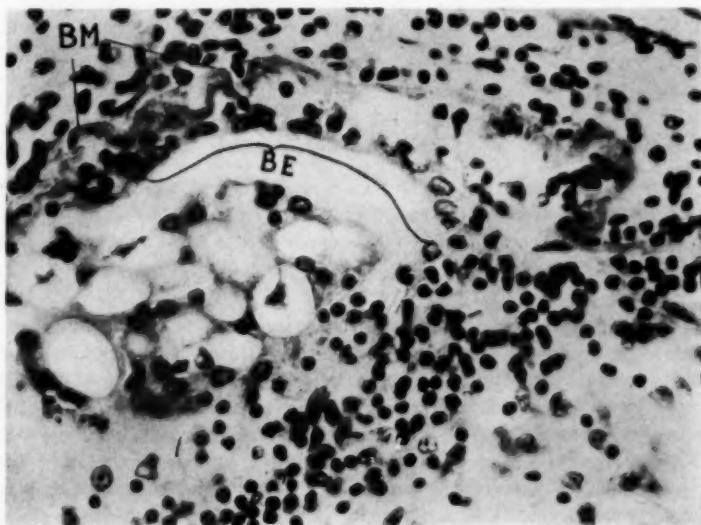


Fig. 4.—Liver of rabbit M2 sixty-four days after infection;  $\times 750$ . *BE* indicates regenerating biliary epithelium in an obliterated bile duct; *BM*, the basement membrane of the former duct.

The parenchymal cells of the liver remained passive even up to quite advanced stages of infection. One rarely saw attempts at regeneration, although marked damage was done to them, especially in the periphery of the lobules. Restoration of these cells, as will be seen later, occurred after the infection had been cleaned up.

Reorganization of the biliary tract set in after further progress had been successfully checked by means of epithelial cells blocking the lumens of the diseased bile ducts. Somewhere within the mass of epithelial cells, usually but not necessarily near the former lining of the plugged duct, there appeared rows of cuboidal epithelial cells that had recovered their previous shape and character (fig. 4).

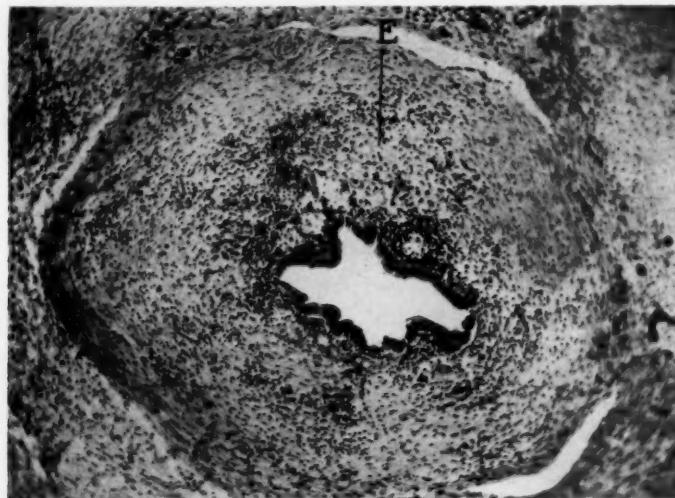


Fig. 5.—Liver of rabbit 157 forty-eight days after infection;  $\times 80$ . A newly formed lumen of a bile duct is shown within an obliterated bile duct. *E* indicates groups of epithelial cells with impacted oocysts of the former duct, situated outside the lumen.

These cells possibly were regenerated from intact parts of the lining or from unaffected small branches or from glands of the former mucosa. Subsequently, a lumen was formed by proliferation and anastomosis of such rows of cells, which at first was much smaller than the original lumen; consequently the majority of cells enclosing the remaining oocysts, which had been situated within the lumen of the original bile duct, were now found outside the newly formed lumen (fig. 5).

The epithelial cells lining these lumens reached the size of columnar cells and had a peculiar uniform and stiff character; the lumens of these ducts gaped, and showed no papilli, so that they often resembled cross-sections of glandular structures. During the process of forming new bile ducts, a part of the material obliterating the former bile ducts was being enclosed within the new lumens and, after the establishment of communication with the common bile duct, was dis-

charged into the intestinal canal. It was characteristic that, from this time on, chiefly nonfertilized and degenerated oocysts appeared in the feces. The groups of cells and oocysts not in contact with the newly formed bile ducts remained in the neighborhood of the new bile channels. Probably owing to their then different position outside the biliary system, they caused a local reaction characterized by granulation tissue and wandering cells, among which polymorphonuclear leukocytes and sometimes eosinophils stood out along with the lymphocytes and plasma cells. Some of the capillaries and fibroblasts as well as wandering cells penetrated the groups of cells in an attempt to organize. Foreign body giant cells were sometimes present enclosing one or more collapsed shells. As a result, the masses of cells were split up into small groups, which in some instances then remained in the neighborhood of the bile ducts for some time. Occasionally calcification occurred, but more often the cells finally disappeared and were replaced by connective tissue, in which an occasional collapsed or deformed oocyst shell was embedded.

The newly formed bile ducts within the obliterated lumens of the former biliary channels represented only temporary structures. Soon they underwent a profound and interesting metamorphosis by which the original caliber was restored. The basement membrane of the former duct, which during the process of obliteration could hardly be made out, became prominent (fig. 4). It appeared as an eosinophilic, undulating membrane which seemed much too long for the new bile channel and often enclosed the groups of cells and oocysts in the neighborhood of the bile duct formerly situated within the lumen of the obliterated biliary channel (fig. 6 A). Sometimes only parts of this membrane, incompletely surrounding a bile duct, were present. Groups of cells and oocysts showing no basement membrane around them probably represented former small bile ducts. This membrane then grew to a thick, hyaline, corrugated band, the loops of which were approached by the provisional epithelial lining of the newly formed lumen of the bile duct, whereby papillary structures were produced (fig. 6 A). The tips of these papilli were usually broad and round, while the stalks were rather narrow, sometimes consisting of only the double basement membrane. In Weigert's elastic tissue preparations this membrane took a grayish-black stain. Owing, most probably, to nutritional difficulties, the tips of the papilli then became necrotic and sloughed off into the lumen.

Groups of cells around oocysts present in the neighborhood of the newly formed papilli, and most of the loops of the thickened and hyalinized basement membrane, were likewise discharged into the lumen of the biliary tract (fig. 6 B). The denuded sections of the lumen were then again covered with epithelium, and adjacent parts of the basement membranes united, forming a thin, continuous line around the epithelial layer of the duct. During this process the mucous glands of larger ducts were regenerated, possibly from groups of invaginated epithelial cells of the newly formed mucosa. The restoration of the intrahepatic bile ducts had then been completed.

The persistence of nodules containing oocysts may be explained by the lack of regeneration of epithelium within obliterated bile ducts, so that no communication between the affected bile ducts and the functioning biliary system existed. These

nodules were then surrounded by connective tissue, and the enclosed oocysts after some time degenerated and could no longer be sporulated; calcification occasionally occurred. Similarly, groups of epithelial cells obliterating infected bile ducts sometimes persisted for a time if no restoration of the lumens of the ducts occurred.

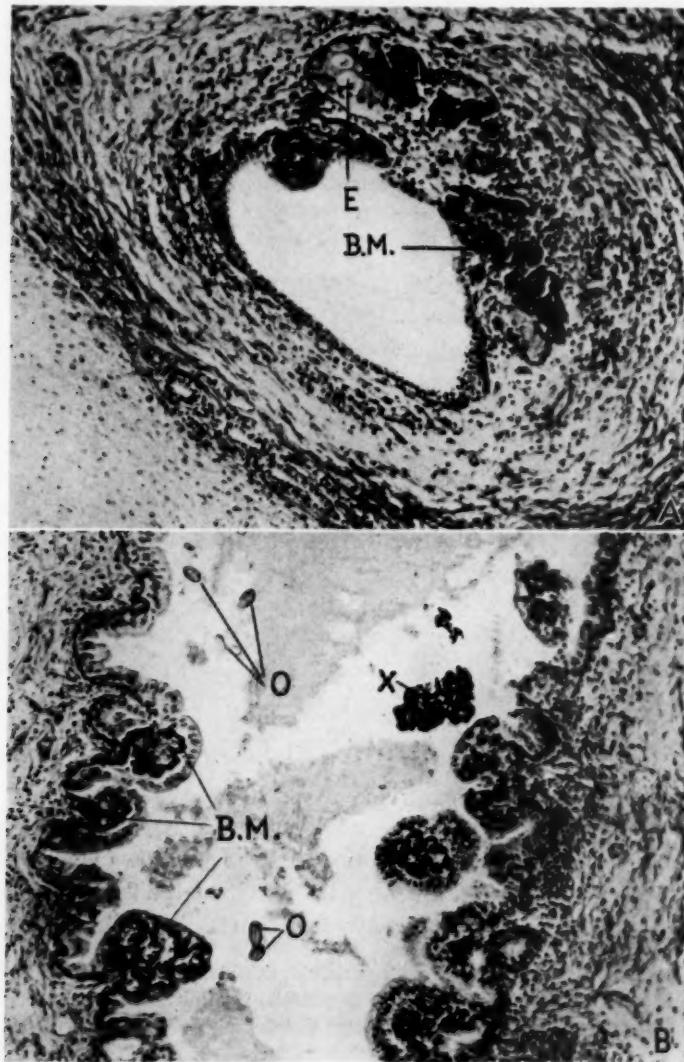


Fig. 6.—Liver of rabbit 127 forty-two days after infection;  $\times 100$ ; Weigert's elastic tissue stain. In A, note the basement membrane (BM) of a former bile duct including epithelial cells (E) and impacted oocysts, situated outside the newly formed lumen. In B, note the basement membrane (BM) of a large bile duct, the formation of papillae due to proliferation of the basement membrane, a necrotic papilla (X) consisting of coils of the basement membrane, and oocysts (O) in the lumen of the bile duct.

Later on these groups were split into smaller parts by ingrowing granulation tissue, which finally resulted in scar tissue containing an occasional deformed oocyst. The reorganization of the biliary channels of such a periportal field was accomplished by the gradual enlargement of the small bile ducts in the vicinity of the former, obliterated duct.

The healing process in the extrahepatic bile ducts was less complicated and began when the process of gametogony was at its height. The papilli holding the infected epithelial cells became necrotic and sloughed off into the lumen, usually causing complete denudation of the mucosa of the duct. This process of necrosis in some instances extended deep into the mucosa, in which case the defect was first replaced by granulation tissue before the lumen could be relined by epithelial cells regenerating from remnants of epithelium or from mucosal glands. A single layer of columnar epithelial cells lined the new lumen of the duct provisionally; no papilli or mucous glands were present at this time, but were regenerated later. The healing process in the extrahepatic bile ducts was sometimes completed before that in the intrahepatic ducts, so that a perfectly normal common bile duct could be found while the process of restoration in the liver was still going on.

After the completion of the regeneration and restoration of the intrahepatic bile ducts, sections of the liver showed a peculiar picture. The parenchyma was traversed by thick bands of scar tissue containing the regenerated bile ducts, and one could still see groups of large, foamy cells around distorted and collapsed shells of oocysts embedded in the connective tissue. The lobular structure of the hepatic tissue was often disturbed, and some of the lobules were surrounded by connective tissue. Many of the enlarged periportal fields lacked the normal relation between bile duct, portal vein and hepatic artery.

It was at this stage that regeneration of the parenchyma of the liver could be studied best. Groups of hepatic cells, characterized by deeper staining of their cytoplasm, usually appeared in the immediate neighborhood of the periportal scar tissue. Their cytoplasm was often drawn out, even spindle-shaped; the sinusoids ran in different directions, sometimes perpendicular to the capillary channels of the neighboring hepatic tissue, and no central vein or any lobular arrangement was present as yet. Mitotic figures of such regenerating cells were not observed, so that their amitotic multiplication must be assumed. The thick septums and scars traversing the hepatic tissue were gradually reduced to thin bands, which in some cases still linked adjacent periportal fields. These fine scars apparently could remain for a long period of time, perhaps even permanently (fig. 8). When found at the same time that oocysts are present in the bile of the gallbladder, they are certain evidence of healed coccidiosis of the liver even if no nodules can be found in any part of the organ. However, there were

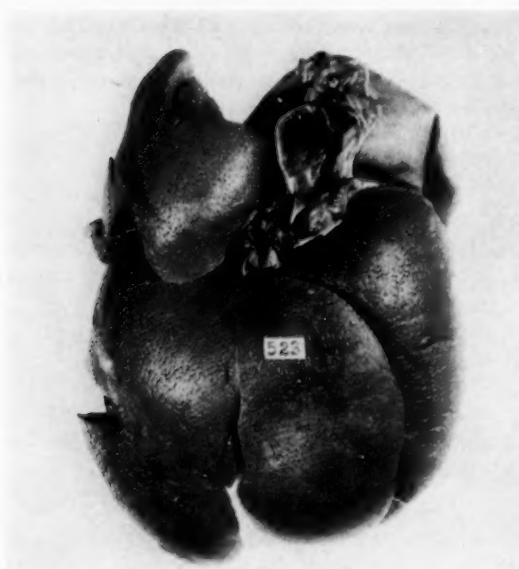


Fig. 7.—Cirrhotic liver of rabbit 523 one hundred and one days after infection. The organ as shown is about one half its actual size.

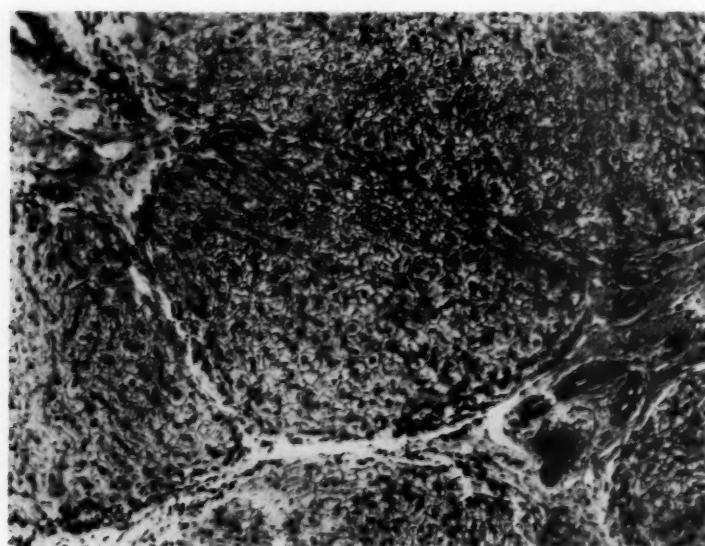


Fig. 8.—A section of tissue from the liver shown in figure 7;  $\times 80$ .

cases in which even the fine scarring disappeared completely, leaving an absolutely normal looking liver, the oocysts in the gallbladder remaining for some time as the sole evidence of the past infection; finally they also disappeared.

The length of time required for the appearance of healing stages after infection varied and also depended on the extent of the lesions; the age of the animal may also have been of importance. Although local signs of healing tendencies—for instance, obliteration of some of the bile ducts by proliferated epithelial cells—were found throughout the stages of gametogony, the generalized regression of diffuse lesions was seen only about from six to seven weeks after infection. This apparently was the critical time, since most of the rabbits with diffuse coccidiosis died from four to six weeks after infection.

In two cases (rabbits 529 and 523), biopsies of the liver were performed in order to study the progress of the healing stages. A piece of liver of rabbit 529 was excised sixty-nine days after infection because of the appearance of only non-fertilized and degenerated oocysts in the feces. The animal was then killed seventeen days after the operation (eighty-six days after infection). The sections of the excised piece of liver showed advanced stages of healing coccidiosis with regeneration and reorganization of bile ducts. In those obtained at autopsy, the reorganization of the biliary channels was practically completed; the bile ducts were surrounded by broad scars which contained a few nests of epithelial cells around collapsed oocysts. A biopsy of the liver performed on rabbit 523 thirty days after infection revealed diffuse coccidiosis at the height of gametogony; a second biopsy, sixty-two days after infection, showed beginning healing with regeneration of the lumens within the obliterated former ducts. Shortly before this second biopsy only nonfertilized and degenerated oocysts appeared in the feces. At autopsy (one hundred and one days after infection) the liver presented the picture of diffuse cirrhosis, grossly and microscopically (figs. 7 and 8).

Diffuse cirrhosis of the liver with regeneration of hepatic cells was also seen in cases of spontaneous coccidiosis; several times, however, a perfectly normal liver was encountered while the bile of the gallbladder contained many oocysts. In such cases it was assumed that the lesions in the liver had completely healed and disappeared.

#### REINFECTION OF RABBITS WITH *EIMERIA STIEDAE*

The question of immunity of rabbits to coccidiosis after recovery from one or several infections has repeatedly been raised. In a large series of animals Bachman<sup>7</sup> was able to demonstrate that rabbits which had had previous infections of *Eimeria perforans* were immune to experimental infection with the same organism, but were not resistant to an infection with *Eimeria stiedae*.

Taking for granted that the presence of oocysts in the gallbladder<sup>8</sup> is the most certain evidence of a present or a past infection of the liver with *Eimeria stiedae*, I studied the effect of reinfection with the same

7. Bachman: Am. J. Hyg. 12:641, 1930.

organism in seven animals; in all but one case a biopsy of the liver was performed, and the gallbladder was punctured, previous to the oral reinfection.

From the results given in table 3 it can be seen that in three of seven cases reinfection was successful.

In one case (rabbit 6) it was doubtful whether the lesions found at autopsy had been produced by the reinfection, or whether they represented healing stages of lesions seen in the sections taken at biopsy forty-two days before death. The liver of rabbit 2 showed only old lesions. No evidence of schizogony that would correspond to the length of time elapsed after the attempt at reinfection could be discovered. No signs of coccidiosis were seen in the liver of rabbit 4. The result of the reinfection in rabbit 1 was also somewhat doubtful, owing to the shortness of time after reinfection.

Although the percentage of reinfection in this small series is slightly below the ordinary, it can definitely be stated that previous infection

TABLE 3.—Reinfection of Liver with *Eimeria Stiedae*

Animal	Age, Weeks	Biopsy of Liver	Oocysts in Bile of Gall- bladder	Dura- tion of Exper., Days	Findings in Liver at Autopsy	Result of Reinfec- tion
1	11	Chronic coccidiosis	+	7	No evidence of coccidiosis	0
2	4	Coccidiosis ?	+	9	Chronic coccidiosis, healing	0
3	10	.....	+	11	Old healed lesions and early schizogony	+
4	12	No evidence of coccidiosis	+	15	No evidence of coccidiosis	0
5	5	No evidence of coccidiosis	+	23	Advanced coccidiosis, game- togeny	+
6	18	Chronic coccidiosis	+	42	Healing coccidiosis, cirrhosis of liver	?
7	10	Chronic coccidiosis	+	60	Advanced coccidiosis, healing	+

with *Eimeria stiedae* does not necessarily result in immunity to experimental infection with the same organism.

#### SUMMARY AND COMMENT

The morphologic studies of coccidiosis of the liver reveal that the earliest lesions appear first in the epithelial cells of the small intrahepatic bile ducts about one week after the oral infection. The primary infection of the distal end of the common duct and subsequent "contact infection" by merozoites moving up into the bile ducts of the liver can be excluded, as the infection of the common bile duct appears later than that of the intrahepatic ducts.

From the outcome of the experiments reported in part II of this study<sup>5</sup> (the Mode of Infection of the Liver) it can be concluded that the portal vein represents the portal of entry to the liver for sporozoites of *Eimeria stiedae*. After their liberation in the duodenum by the pancreatic juice, the sporozoites penetrate into the mucosa of the intestine, enter a blood vessel and are carried into the liver by the blood stream.

In the portal spaces, they leave the blood vessels and by their active movements traverse the tissue and reach the epithelial cells of the bile ducts from without.

It was pointed out (p. 520) that bodies resembling sporozoites in every respect were seen in the tissues surrounding bile ducts in sections obtained in the earliest case of coccidiosis of the liver, six days after infection. Although there is no means of absolutely proving their identity, the presence of such bodies supports the theoretical considerations and is in harmony with the outcome of the experiments.

Once the sporozoites have reached the epithelial cells of the bile ducts, the course of the disease is easy to follow and to understand.

Theoretically speaking, a single sporozoite can cause diffuse coccidiosis of the liver. If one assumes with Reich<sup>2</sup> that the asexual cycle can be repeated several times before gametogony sets in, and that sixteen merozoites are formed in one cycle, one sporozoite could then produce over one million merozoites in five cycles of schizogony; this rapid multiplication of the parasites explains the tremendous speed with which the infection spreads through the biliary system, leaving hardly any epithelial cell intact; the effect of the regeneration of cells is nullified by the immediate infestation of the newly formed cells by the swarming parasites. Drifting in the bile, the schizonts infect the epithelial cells of the larger bile channels and the extrahepatic ducts down to the entrance of the common bile duct into the duodenum. The epithelium of newly formed bile ducts likewise becomes contaminated as soon as communication with infected ducts is established.

Isolated scanty lesions can be explained by assuming that very few sporozoites succeeded in reaching the liver, and that the process exhausted itself before a large territory became infected; this is probably the case in natural infections caused by sporadic oocysts in contaminated food.

With the beginning of gametogony, the spreading of the process is retarded, as one schizont forms only four merozoites, which develop into either macrogametocytes or microgametocytes.

The final extent of the infection is reached when all the merozoites of the sexual cycle are lodged in epithelial cells. From then on, only maturing macrogametocytes and microgametocytes inhabit the epithelial cells, and no new infection of cells can take place. Mature macrogametes are fertilized by the swarming microgametes and develop into oocysts, which are liberated from the remnants of epithelial cells and may be discharged through the biliary channels into the intestines.

It is usually at this stage of the exhaustion of the process that animals die, but healing can occur if they survive. The healing process does not take place all at once throughout the liver, but attempts at

checking the infection can be seen in places during the entire cycle of gametogony.

It has been pointed out that the epithelium of the bile ducts accomplishes then the complete arrest of any further progress by plugging the lumen; in this way, the gametocytes still present in some of the cells are destroyed, and the microgametes are prevented from reaching the macrogametes, so that the latter cannot be fertilized.

The evidence for the epithelial nature of the peculiar large, foamy cells which fill the bile ducts at this stage is as follows: the presence of mitotic figures in lining cells before the proliferation takes place; the similarity of the nuclei of these cells to those of normal lining cells; the confinement of the proliferation within the basal membrane of the former ducts; the absence of capillaries characteristic of granulation tissue, and the apparent capacity of these cells to recover their former character as lining cells.

The effect on the parasites of the proliferated epithelial cells that block the lumens of the affected ducts is striking and can be clearly recognized by examining the feces of animals during this stage: practically only degenerated and nonfertilized oocysts instead of normal fertilized oocysts are discharged.

After the infection has been stopped successfully, regeneration of the obstructed bile ducts and subsequent reorganization of the biliary channels take place. At first, a provisional lumen is formed, which is lined by cuboidal cells, and which is situated within the mass of cells obliterating the former lumen of the duct. It often seems as though these lining cells originate from cells obstructing the lumen, but the possibility of their regeneration from remaining unaltered cells of the former lining, from intact adjacent ducts or from glands of the former mucosa cannot be excluded.

The masses of epithelial cells surrounding oocysts, formerly situated within the ducts, are now outside the lumens of the newly formed ducts; it is interesting to observe that, owing to their change in position, they are now treated as foreign bodies and can be attacked by granulation tissue, which penetrates the groups of cells, dividing them into smaller parts. Remnants of such groups of cells, often surrounded by foreign body giant cells, remain for some time in the neighborhood of the newly formed bile ducts until they finally disappear. The reorganization of each of the provisional biliary channels is then guided and influenced by the basement membrane of the former duct, resulting in the restoration of the original caliber of the duct.

The areas formerly occupied by the distended bile ducts are now transformed into thick bands of fibrous tissue diffusely traversing the hepatic tissue; the newly formed biliary channels are embedded in this scar tissue. Gradually, owing to regeneration of parenchymal cells of

the liver, the thick bands are split and reduced to finer bands, which still may extend from one periportal field to another, often completely surrounding individual hepatic lobules.

The gross appearance of the liver at this stage is that of diffuse cirrhosis without jaundice. Microscopically, it somewhat resembles biliary cirrhosis without, of course, showing the retention of bile and the distended bile capillaries. Owing to the peculiarity of the coccidiosis affecting primarily the biliary epithelium and only secondarily the portal canals and the hepatic tissue, this cirrhosis is, of course, histogenetically different from the cirrhosis occurring in man; the final stage of the process, however, leading to increase of interlobular connective tissue, new formation of bile ducts and formation of pseudolobules, cannot be differentiated from true cirrhosis. At this stage, the only evidence of the nature of this cirrhosis is that offered by the presence of oocysts in the bile of the gallbladder.

A varying amount of brownish granular pigment in Kupffer cells, in parenchymal cells of the liver and in the portal connective tissue was occasionally seen in livers of the normal rabbits, as well as in those showing different degrees and stages of coccidial infection including cirrhosis. As there seemed no relation between this pigment and the problem, no attention was paid to its presence or absence, especially since carrots were a part of the diet of the animals.

It is important to be familiar with the picture of cirrhosis of the liver in the rabbit due to coccidiosis, as this disease is extremely common, even in apparently healthy stock. Because of the frequency and because of the noncharacteristic nature of this disease, the rabbit would not appear to be the most desirable animal for experimental production of cirrhosis unless coccidiosis of the liver could be excluded with certainty.

In spite of this, however, most of the experimental work done on cirrhosis of the liver, especially pigmentary cirrhosis due to copper,<sup>8</sup> has been carried out on rabbits or, at least, such work has apparently been more successful in rabbits than in any other animal. Little attention has been paid to the coccidial infection and its consequences in the livers of the experimental animals, and control examinations of pieces of liver obtained for biopsy have been reported only by Flinn and Von Glahn.<sup>se</sup> Hall and Butt,<sup>sb</sup> working with rabbits, rats and sheep on experimental pigmentary cirrhosis due to copper poisoning, mentioned the possibility of coccidiosis as a cause of bile duct proliferations in rabbit 5, table 1, of their report. Hall and MacKay,<sup>se</sup> working with rabbits on experimental hepatic pigmentation and cirrhosis, stated, on page 332 of their paper, that "many of the animals showed some coccidial infestation. If one of a pair was infested, the litter mate was usually also infested. In any case this factor appeared to have little influence on the final result."

8. (a) Mallory, Parker and Nye: J. M. Research **42**:461, 1921. (b) Hall and Butt: Arch. Path. **6**:1, 1928. (c) Flinn and Von Glahn: J. Exper. Med. **49**:5, 1929. (d) Polson: Brit. J. Exper. Path. **10**:241, 1929. (e) Hall and MacKay: Am. J. Path. **7**:327, 1931.

From the studies of my material it seems imperative to exclude with absolute certainty coccidiosis of the liver as a possible cause of the experimental cirrhosis; this, however, appears to be practically impossible.

#### CONCLUSIONS

The earliest recognizable lesions of schizogony in the liver occur about one week after infection.

Gametogony sets in about two weeks after infection, and both cycles—schizogony and gametogony—are present at the same time until about three weeks after infection; from then on, only gametogony is found.

Even diffuse experimental coccidiosis of the liver is not necessarily fatal; healing can take place after the exhaustion of gametogony, and is accomplished by the blockage of infected bile ducts by proliferating epithelial cells, followed by regeneration and reorganization of the biliary channels.

The healing stage is characterized by the appearance of degenerated and nonfertilized oocysts in the feces.

Diffuse cirrhosis of the liver may be the end-result of coccidiosis of the liver.

Previous infection of the liver with *Eimeria stiedae* does not necessarily result in immunity to experimental reinfection.

Because of the frequency of coccidial infection of the liver, resulting sometimes in cirrhosis, the use of rabbits for work on experimental cirrhosis of the liver cannot be recommended.

## Laboratory Methods and Technical Notes

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### FLUORESCENCE OF CARTILAGE EXPOSED TO FILTERED ULTRAVIOLET RADIATION

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Fluorescence of tissues or of other substances, organic and inorganic, is excited by the longer wavelengths of ultraviolet rays. The filter of nickel oxide glass excludes visible light and the shorter ultraviolet wavelengths. The best fluorescence is obtained with wavelengths ranging from 300 to 400 millimicrons, the strongest spectral lines being at 366 millimicrons. An object exposed to these waves of invisible radiation fluoresces after a very brief interval of lagging. The fluorescence may be an alteration of color, as with eosin, which in daylight is pink, and in filtered ultraviolet radiation, a golden yellow. Or there may be an increase in intensity of color as with methylene blue; not infrequently a substance will not fluoresce, as phenolsulphonphthalein.

Few body tissues exhibit definite fluorescence. The more compact and solid structures of the body fluoresce better than the looser, less solid tissues. Thus, teeth, bone, cartilage and tendon give forth definite fluorescence, while liver, intestine and spleen exhibit only mild indefinite fluorescence. This fluorescent change has been used in the interpretation of skin diseases, especially of anomalies of pigmentation, and also in ophthalmology in the recognition of corneal and lenticular lesions.

The fluorescence of fresh tissues varies from that of decaying or preserved tissues. Young tissues may fluoresce differently from old ones. In beginning decay, tissues that ordinarily fluoresce bluish become more or less greenish. The hemoglobin content of a tissue alters its fluorescence, an increase of hemoglobin causing a shift in color to brown.

The purpose of this study was to investigate the fluorescence of a healthy and of diseased hyaline joint cartilage and to show that there is a selective fluorescent differentiation between diseased, especially eroded, areas in cartilage and normal cartilage. The fluorescence of dye-stained cartilage is also considered. Three human knee joints of amputated limbs, six knee joints of three guinea-pigs and twenty-four knee joints of twelve rabbits, in eighteen of which an experimental traumatic erosion had been produced, were examined. A few other animal joints—shoulder, elbow and hip—were also examined, making a total of thirty-nine joints investigated. The opened joints, excised or *in situ*, were placed on the stage of the boxlike examining apparatus. Examination was always conducted in a dark room.

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From the Laboratory Division of the Hospital for Joint Diseases.

Aided by a grant from the Committee on Scientific Research of the American Medical Association.

The normal fluorescence of young, healthy cartilage is a clear, uniform, light blue; occasionally a rose pink is added to it. Elevated areas in cartilage, as the cartilage of the femoral condyles, fluoresce better than depressed areas of cartilage, as the cartilage of the intercondyloid fossa. Thus, every part of a joint does not fluoresce equally well at the same time, those parts covered by fat or other soft tissues or away from the light not lighting up at all. In a joint that is somewhat decayed, as by putrefaction after death, the cartilage loses much of its clear blue fluorescence and takes on a dirty green color. This is a change of decay and not of disease.

Cartilage stained by dyes injected intra-articularly gives forth the fluorescence of the dye and loses its own distinctive color. With most dyes, as with methylene blue, gentian violet and isamine blue, there is merely an intensification of the color of the dye; with dyes such as eosin or mercurochrome there is a fluorescent change corresponding to the fluorescent change of the dye. The intensity of fluorescence also varies with the strength of the dye, a weaker solution, as a 0.05 per cent solution of eosin, not exciting the characteristic golden-yellow color, but producing a mild intensification of the pink eosin color. The intensity of the fluorescence of dye-stained cartilage is also less from three to seven days after injection, the dye coating of the cartilage having been gradually removed either by absorption or by wearing away, since the penetration of stain is always superficial. Fixation of dye-stained joints in formaldehyde results often in loss of dye fluorescence (especially with mercurochrome), but the normal blue fluorescence of cartilage is not altered.

Experimentally and naturally induced areas of disease in cartilage fluoresce differently from normal cartilage. A fresh fracture in cartilage that does not reach to bone marrow does not show alteration of the characteristic bluish color; if it reaches to bone marrow, it is dark red at its base, the color of the marrow being intensified. The fluorescence of diseased areas in cartilage, especially erosions, may be divided into two simple categories, that of areas not reaching to bone marrow and that of areas reaching bone marrow. In either event, the outline of the erosion stands out clearly. If marrow forms the base of the erosion or ulcer in cartilage, the fluorescence of the base is dark red or dark blue, the cartilage about the erosion being dark blackish, at times forming a blue-white band, and not lighting up in its typical blue. If the erosion is superficial, it stands out clearly as a dark area in a lighter field; that is, it is selectively visualized. If the cartilage is diseased in toto, if it is whiter and more opaque than normal, the normal blue fluorescence is lost, and the cartilage stands out as chalky white, with or without distinctly demarcated areas of erosion. Osteophytic enlargements, covered by cartilage, do not show altered fluorescence. Areas of cartilage, covered with fibrin, as a fibrin-covered erosion, give dark brown fluorescence, the color of the fibrin being intensified. If cartilage has been eroded by pus and is covered by new exudate, the blue fluorescence of cartilage is lost and replaced by a dirty green-gray color.

The structures within a joint fluoresce variously. In the knee joint, the crucial ligaments fluoresce steel white and the semilunar cartilages pure white. The semilunar cartilages, as all other structures within a joint, when dye-stained, assume the fluorescence of the dye. Synovia

gives a very mild, bluish fluorescence, and when dye-stained, assumes the color of the dye. Fat is a clear yellow-white. The cut end of a bone is steel white in its compacta and dark red or brown in its medulla. Tendon is clear white. Muscle gives a velvety brown fluorescence, which may alter on standing or on admixture with dye; thus in muscle infiltrated by mercurochrome there is an alteration of the velvety brown color to a dark green in from fifteen to twenty minutes. The capsule of the knee joint may stand out well in a dye-stained joint, especially the posterior capsule when viewed from behind, after intra-articular injection of eosin or mercurochrome.

#### SUMMARY

The fluorescent action of filtered ultraviolet radiation on normal cartilage, both stained and unstained, and on experimentally and naturally diseased cartilage, has been described. It is found that diseased areas in cartilage, especially areas of erosion, fluoresce differently and stand out prominently from normal cartilage, especially when not stained. There is no particular advantage in staining cartilage for fluorescent diagnosis. It does not bring out diseased areas the better and coats cartilage so as to lessen the recognition of diseased areas.

It is planned to construct an instrument similar to the arthroscope, containing a source of ultraviolet rays of small size, as described by Westmann<sup>1</sup> and by Saidman.<sup>2</sup> By filtering the ultraviolet rays by a proper filter at the point of their emergence, it will be possible to study fluorescence of cartilage in the closed joint and to use this method as a supplement to ordinary arthroscopy.

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1. Westmann, Stephan: *Med. Klin.* **26**:1146, 1930.
2. Saidman, Jean: *Bull. Acad. de méd., Paris* **93**:282, 1925.

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#### A LIVE STEAM INSPISSATOR ATTACHMENT FOR THE AUTOCLAVE

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In the preparation of inspissated egg medium for growing tubercle bacilli, we have observed that the manner of inspissation of the medium has a great deal to do with its quality. The temperature in different parts of the inspissator, if not carefully watched, varies a great deal, and the result is a poor product. This was found to be true with the old Koch type of inspissator. In the "dry" (electrically heated) types of heaters, the temperature varied from 5 to 8 C. from point to point in the instrument, and besides, these types dehydrated the medium beyond use. Many years ago it was found that by the use of a jet of live steam carefully admitted into an upright type of inspissator, a

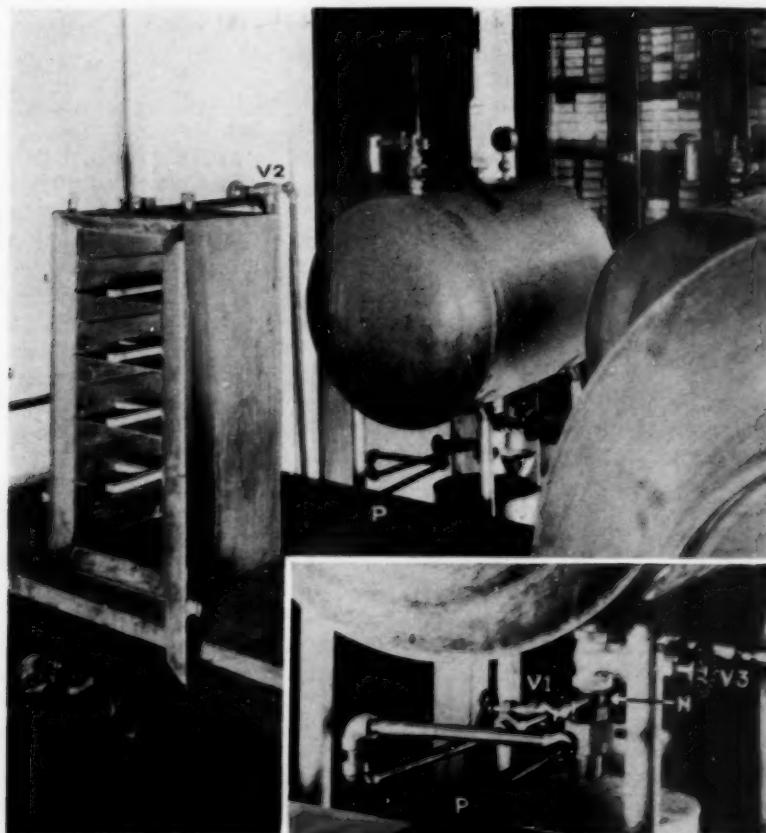
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From the Research Laboratories of the Chicago Municipal Tuberculosis Sanitarium.

temperature could be maintained constant within 2 C. in all parts of the instrument. Many laboratories, however, have not the access to live steam. Accordingly, we have devised a method that will permit the attachment of the upright inspissator to any autoclave.

#### THE INSPISSATOR AND STEAM HOOK-UP

The inspissator<sup>1</sup> is a double-walled copper or monel metal box with outside dimensions of 10½ inches (26.3 cm.) in depth, 13 inches (32.5 cm.) in width and



Inspissator and steam hook-up: *N*, nipple; *P*, steam pipe; *V1*, *V2* and *V3*, valves.

24½ inches (61.25 cm.) in height, and inside dimensions of 8 inches (20 cm.) in depth, 10½ inches (26.25 cm.) in width and 22 inches (55 cm.) in height. The full length door opens on the side and is beveled to make it fit close and to have a 1 inch (2.5 cm.) air space between the outer and inner walls. The inside chamber is equipped with nine perforated metal shelves. An overflow glass tube shows

1. This attachment, together with other equipment for this type of culturing, may be obtained from the Central Scientific Co., Chicago.

the amount of water in the tank and prevents overexpansion from the steam supply. The steam is connected by means of a one-fourth inch (0.61 cm.) iron pipe which enters at a posterior corner and extends to within 2 inches (5 cm.) of the bottom. The generator of an ordinary horizontal type of autoclave may be used for the purpose of furnishing the live steam and has been run successfully by the following hook-up, which does not interfere with the use of the autoclave even when it is desirable to run both simultaneously.

Immediately above the generator, a nipple, "N," is inserted and tapped for a three-eighths inch (0.9 cm.) steam pipe, "P," leading to the inspissator. A valve, "V1," should be inserted close to the autoclave so that the steam may be shut off from the inspissator when not in use. Another valve, "V2" should be inserted at the junction of the steam pipe and the inspissator to use as a regulator for the control of steam entering the inspissator, because only a small amount is required. (Caution: At least three elbows must be used between the autoclave and the inspissator to prevent the rush of high pressure steam from bursting the pipes.) Another valve, "V3," is inserted above the nipple leading to the inspissator to control the steam leading into the tank of the autoclave. This valve makes it possible to run the inspissator independent of the autoclave, but better results are obtained by carrying from 3 to 5 pounds (1.4 to 2.3 Kg.) pressure on the autoclave during the running of the inspissator.

## General Review

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### PRESENT STATUS AND FUTURE DEVELOPMENT OF LEGAL MEDICINE IN THE UNITED STATES

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#### SYNOPSIS

Definition of Legal Medicine

The Office of Coroner

The Office of Medical Examiner

The Amount and Character of the Work Done by the Coroner and by the Medical Examiner

Authority of the Coroner in Nonviolent Deaths

Psychiatry and the Law

Expert Testimony and the Hypothetic Question

Foreign Institutes of Legal Medicine

Medicolegal Institutes in the United States

Possibilities for Development of Legal Medicine in Certain Localities

State Universities and Institutes of Legal Medicine

Medical Economic Aspects of Legal Medicine

Legal Medicine as a University Discipline

Summary

The results of a study that I undertook for the committee on medicolegal problems of the National Research Council have been published<sup>1</sup> as bulletin 87 of the National Research Council. The purpose of this study was to evaluate the present status of legal medicine in the United States, as exemplified by conditions in certain selected localities. On the basis of existing conditions, lines of development were suggested that would lead to a more complete utilization of medical science in the administration of justice. This article is based on the material contained in bulletin 87.

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1. Schultz, O. T.: Possibilities and Need for Development of Legal Medicine in the United States, with a Supplement on University Departments in the Field of Criminology, Washington, D. C., National Research Council, 1932, bulletin 87.

## DEFINITION OF LEGAL MEDICINE

The term "legal medicine" seems almost to define itself and to need little discussion. But, as Oertel<sup>2</sup> pointed out in a discussion devoted primarily to the status of legal medicine in Canada, which is equally applicable to conditions in the United States, the term "is employed with different meanings. The most common definition is that it is the application of expert medical knowledge to the needs of law or justice. In this definition is embraced, not only criminal law, but the application to all kinds of insurance (life and accident), employees' compensation acts, soldiers' rehabilitations, and other civil procedures. A second, rarer definition applies the term to the social and legal position and relations of the physician himself, that is, his rights, duties, obligations, and responsibilities to the community and to his fellow practitioners, and how the law of the country affects him in the pursuit of his professional practice."

While Oertel's second definition may be the rarer, the law of medicine, that is, law applied to medicine, is a fairly well delimited subdivision of the law and has to do with the statutes and regulations relating to medical licensure and medical practice and with the legal principles relating to malpractice. As medical jurisprudence this aspect of legal medicine is taught in law schools and medical schools and is included in the examinations for medical licensure.

The legal medicine of Oertel's first definition, which is medicine applied to the law, and which might be thought of as forensic medicine, to distinguish it from medical jurisprudence, has a much less clearly defined position in the United States. It is with this aspect of legal medicine that this article deals. The subject matter is the medical investigation of dead persons and the psychiatric study of living persons in the interests of judicial administration. It is necessary to consider also how the results of such investigations may be presented to the agencies of justice.

## THE OFFICE OF CORONER

Except in a relatively small number of jurisdictions in the United States, the investigation of deaths that may have been due to violence is made by the coroner. The importance of the duties of this officer in determining the cause of a death for which some one may be held criminally responsible ought to be self-evident. The cause of death must be accurately determined, and causes of death other than the supposed

2. Oertel, Horst: *The Academic Position of Legal Medicine in Canadian Universities, Institutes of Legal Medicine, Methods and Problems of Medical Education*, ser. 9, New York, the Rockefeller Foundation, Division of Medical Education, 1928, p. 23.

violent one must be excluded. Such work requires postmortem examination, which falls within the special province of the experienced pathologist. If the necropsy is to yield accurate results, and the administration of justice should be content with nothing less, microscopic examination of tissues, bacteriologic investigation and chemical examination for suspected poisons may be necessary. Such complete investigation may not be necessary in every case of a supposedly violent death, but the coroner or his pathologist should know when special investigation is necessary and should have the facilities for it.

It is not necessary to point out in detail here the degree to which the average coroner's office falls short of the desired accuracy. That has been done for a number of localities that may be considered representative of different parts of the country. Investigations of the functioning of the coroner's office in Cleveland,<sup>3</sup> in New York City<sup>4</sup> before the replacement of the coroner by the medical examiner, in Missouri,<sup>5</sup> in Chicago, New Orleans and San Francisco,<sup>6</sup> and in Chicago, Philadelphia and Cincinnati<sup>1</sup> have shown that the thanatologic work of the office leaves much to be desired.

The reasons for the poor performance of duties are not far to seek. On the basis of those reasons the possible inefficiency of an individual coroner may be excluded as of relatively little importance. It is not the official who is at fault, but the system. A coroner's office brought from the sparsely settled rural districts of England may have met adequately the medicolegal needs of the even less densely populated original colonies. Since those early days changed conditions have complicated the problem of crime. The office of coroner, which is often the first investigative governmental agency at the scene of a crime, has not kept pace with its changing environment; it does not fit into the conditions of contemporary civilization. In most states, the statutes establishing the office and defining its duties and powers have remained essentially unchanged.

The office is an obscure one in our political system and does not attract the more robust type of politician. It is an elective office with a short tenure. In most jurisdictions it requires no especial qualifi-

3. The Coroner's Office, Efficiency Series, report no. 2, Municipal Association of Cleveland, 1912. Adler, Herman N.: Medical Science and Criminal Justice, Cleveland Foundation Survey of Criminal Justice in Cleveland, 1921, pt. 5.

4. Wollstein, L. M.: Report on Special Examination of the Accounts and Methods of the Office of Coroner in the City of New York, 1915.

5. Moley, Raymond: The Sheriff and Coroner, Missouri Crime Survey, pt. 2, New York, The Macmillan Company, 1926.

6. Schultz, O. T., and Morgan, E. M.: The Coroner and the Medical Examiner, Washington, D. C., National Research Council, 1928, bull. 64.

cations, although the inquest and the autopsy demand specialized training in law and in medicine, if the magisterial and the medical functions are to be performed as well as they should be.

Those defects dependent on the elective character of the office of coroner are overcome, theoretically at least, by making the office appointive. In Virginia, the judge of the corporation court or of the circuit court appoints a physician "who shall be the coroner" for a period of four years. In West Virginia, the county court appoints the coroner, "who shall hold office during the pleasure of the county court." In Connecticut, the coroner, who must be a qualified attorney-at-law, is appointed for a period of three years by the judges of the superior court. In California, the new charter of San Francisco County, which became effective at the beginning of 1932, removed the office of coroner from the group of elective offices and made the coroner appointive; the tenure is for life or during good behavior.

That the office of coroner is not essential to the American form of government is evident from the fact that the office does not exist or has been abolished in certain states. The performance of the duties of coroner by some other agency of local government in some of these states appears to be based on the assumption that these functions are of minor importance to society. In Arizona, Florida, Nevada, New Mexico, Texas, Utah and Vermont, the work of the coroner is performed by local justices of the peace. In Nebraska, the duties of the coroner have been delegated to the county attorney. In the state of Washington, the prosecuting attorney functions as coroner in counties with a population of less than 40,000. Such transfer of the coroner's duties has certain theoretical advantages. It does away with a minor elective office, and it places the magisterial functions of the office in the hands of officials whose normal duties are magisterial or legally investigative. But so far as the justice of the peace or the county attorney or the prosecuting attorney must work under antiquated laws, and so far as the medical duties are performed by physicians named for the individual case by an official who may have difficulty in evaluating the qualifications necessary for the proper performance of medicolegal work, the method under consideration would appear to be no improvement over the coroner system.

In certain other jurisdictions, the abolition of the office has been based on a recognition of the importance of the medicolegal duties of the coroner and on the belief that those duties should be performed by medically trained persons who are qualified to do them well. In both theory and practice, the medical examiner system is a decided improvement over the coroner system.

## THE OFFICE OF MEDICAL EXAMINER

Massachusetts replaced the coroner by the medical examiner in 1877 and placed the medicolegal duties usually entrusted to the coroner in the hands of qualified physicians. The magisterial functions were transferred to the district attorney and other existing agencies. The medical examiners are appointed by the governor.

Other New England states followed the lead of Massachusetts. In Connecticut, the office of coroner is retained for the holding of inquests. The coroner, who, as already noted, is appointed and must be an attorney, names the medical examiner. In Maine and Rhode Island, the governor appoints the medical examiners for periods of four and six years, respectively. In New Hampshire, the medicolegal officer is termed a medical referee; he is appointed by the governor for a period of five years.

In 1915 the legislature of New York abolished the office of coroner in New York City and substituted the office of chief medical examiner. The change became effective in January, 1918, when the authority of a single chief medical examiner, who has been serving continuously since that time, replaced that of the several coroners whose jurisdictions entered into the formation of the greater city.

In 1927 New Jersey made the adoption of the medical examiner system optional with the two counties of the first class. The change was immediately made by Essex County, in which Newark is located. The New Jersey act is quoted in full by Weinmann.<sup>7</sup> In its definition of medicolegal duties that directly concern the public, and in its definition of the authority of the medical examiner in the performance of those duties, this act is a model that should be followed by other jurisdictions.

Is the medical examiner system in its actual functioning under everyday conditions an improvement over the coroner system? After comparing the two systems, Schultz and Morgan,<sup>8</sup> in summarizing the description of the medical examiner's office of New York City, said:

The contrast between this account and the story of New Orleans, San Francisco, and Chicago is in many respects impressive. In the field of criminal justice it is startling. The organization for instant investigation, the character and ability of the personnel, . . . the thoroughness of the examination, and the accuracy and completeness of the records—all these make for certainty, so far as humanly possible, that the cause of death will be correctly determined and that the means of demonstrating it to a court and jury according to the forms of law will be made available to the proper prosecuting officers.

7. Weinmann, G. H.: A Compendium of the Statute Law of Coroners and Medical Examiners in the United States, Washington, D. C., National Research Council, 1932, bull. 83, p. 218.

Further study of the office of medical examiner of New York City and of that of Boston, together with a review of the work of the more recently established office of medical examiner of Newark, serves only to emphasize the superior functioning of this system as compared with the coroner system.

The medical examiner system is not perfect. The thoroughly competent scientists who administer the medical examiners' offices of New York City, Boston and Newark would be the last to lay claim to perfection in the work of their offices. They are more cognizant than any one else of the shortcomings of their offices. These shortcomings are not due to the system or to the laws underlying the system, or to the scientific personnel that administers the system. The people of these communities have admitted the importance of legal medicine in the administration of justice by adopting the medical examiner system. They fall short of recognizing the full significance of legal medicine to the extent that they withhold the financial support that would enable their medical examiners to utilize every scientific aid in the interest of society.

A measure of the comparative value of the office of coroner and of that of medical examiner is given by the scientific thoroughness with which the work is done, that is, by the quality of the work. The quality of the work cannot, however, be accurately determined and, so far as the offices under discussion are concerned, is influenced by a number of factors. Chief among these are the scientific attainment and experience of the personnel. These will depend, in turn, on the initial scientific qualifications of the medical personnel, on the continuity and length of service, on freedom from political interference, on the facilities provided for scientific work and on the legal definition of their authority. In all of these respects, comparison is wholly in favor of the medical examiner system. Judgment of the quality of the work will be influenced also by the records of the office, by their value as scientific documents and as documents that contain information that may be submitted in evidence. In this respect, also, the work of the medical examiner's office is of a uniformly much higher quality than that of the average coroner's office.

#### THE AMOUNT AND CHARACTER OF THE WORK DONE BY THE CORONER AND BY THE MEDICAL EXAMINER

Some idea of the value of the office of coroner and of that of medical examiner as medicolegal agencies for the administration of justice may be obtained from the amount of work that each office is called on to perform and from the proportionate distribution of the work among the several categories into which the referred cases fall. In the complete

study on which this article is based, a table is given summarizing the work of the medical examiners' offices of New York City, Suffolk County (Boston), Mass., and Essex County (Newark), N. J., and of the coroners' offices of Cook County (Chicago), Ill., Philadelphia and Hamilton County (Cincinnati), Ohio. This table is reproduced on page 549.

The total work done by a coroner's or a medical examiner's office will depend primarily, of course, on the population of the jurisdiction served by the office. The populations of the jurisdictions included in the table ranged from 589,356 for Hamilton County to 6,300,000 for New York City. The total number of cases referred to the coroner or medical examiner for investigation varied correspondingly; it ranged from 1,336 for Hamilton County to 14,954 for New York City. But these total figures, although they may give a measure of the relative importance of the various offices, do not give a true measure of the value of any particular office to its community. In the various jurisdictions under consideration, the mortality may be accepted as practically the same. In each of these jurisdictions, a certain, approximately proportionate number of persons will die, and of the deaths a certain number will be referred to the coroner or medical examiner for investigation. The proportion of the total number of deaths referred to the office therefore gives a better measure of the relative value of each of the various offices to its community than does the total number of deaths investigated. With this method of comparison, it is seen that the percentage of deaths investigated by the medical examiners' offices varied from 12 to 19.7, with an average of 17 per cent. The percentage of deaths referred to the coroner's office varied from 9.7 to 20.9, with an average of 15.8 per cent.

The relatively low percentage, 9.7, of deaths that were investigated by the coroner's office of Cook County was the result of local conditions, namely, a conflict between the vital statistics law and the laws relating to the coroner's office, and an opinion of the local state's attorney's office that the coroner's jurisdiction is limited to deaths due to violence or undue means. Because of the effect of these local conditions on the distribution of cases investigated, the Cook County office will be omitted in the further consideration of the figures.

Study of the distribution of the various kinds of cases referred to the office of coroner or medical examiner for investigation brings to light some interesting facts. Deaths due to criminal homicide, the investigation of which was probably one of the main principles underlying the original development of an agency like that of the coroner's office, averaged 3.4 per cent. In the mind of the prosecuting official, the

*Summary of the Work of the Offices of Medical Examiner and Coroner in Selected Communities*

Medical Examiner	Year	Population	Cost per 100,000	Deaths				Violent Deaths				Abortion				Natural Causes				
				Total	Referred	Per Cent	Homicide	Per Cent	Suicide	Per Cent	Casualty	Per Cent	Total	Per Cent	Total	Per Cent	Total	Per Cent		
				1929	1930	1930	1930	1929	1930	1930	1930	1929	1930	1930	1930	1929	1930	1930	1930	
New York City.....	1929	6,390,000	\$2,646	77,482	14,054	19.3	426	2.8	1,312	8.8	4,536	30.3	6,274	41.9	118	0.8	7,582	50.8	3,003	20.1
Suffolk Co., Mass., (Boston)	1930	879,596	5,077	12,965	1,471	12.0	23	1.6	128	8.7	571	38.8	722	49.1	11	0.7	734	49.9	283	19.2
Essex Co., N. J. .... (Newark)	1930	833,513	6,115	9,010	1,775	19.7	62	3.5	145	8.2	508	32.0	775	43.7	19	1.1	874	49.2	869	48.4
Coroner																				
Cook County, Ill., (Chicago)	1930	3,469,123	3,575	42,020	4,098	9.7	521	12.7	730	17.8	2,794	62.3	3,815	93.8	44	1.1	209	5.1	1,530	37.3
Philadelphia.....	1930	1,904,451	5,056	27,660	5,774	20.9	102	2.8	311	5.4	1,815	31.4	2,288	39.6	53	0.9	3,433	50.4	1,452	25.1
Hamilton Co., Ohio (Cincinnati)	1930	589,356	4,256	7,943	1,326	16.8	87	6.5	127	9.5	545	40.7	759	56.7	9	0.7	568	42.5	191	14.3

investigation of homicidal deaths is still the main reason for the existence of an agency like the office of coroner or medical examiner, but the minor importance of this group numerically would appear to indicate that society has need of an agency that must investigate many deaths other than those due to criminal homicide.

The necessity for the investigation of suicidal deaths, which averaged 8.1 per cent, will probably be granted by every one. For society as a whole, this group is important because a decision must be made as between the homicidal or the suicidal character of these deaths. For individual members of society, a decision as between suicide and casualty may be important in the collection of life or accident insurance.

Other forms of violence, grouped together under casualty, caused from 30.3 to 40.7 per cent of all the deaths referred to the coroner or medical examiner. The average was 34.6 per cent. Society has an interest in these deaths, because a differentiation must be made between homicide and accident, and because the casualty may be due to the criminal or negligent act of another. The importance of this group in the administration of workmen's compensation acts and in the collection of claims for insurance of one form or another is evident.

All forms of violence together made up from 39.6 to 56.7 per cent of the work of the five offices. The average was 46.2 per cent. Reading of the statutes creates the impression that the investigation of violent deaths is the main function of the coroner's office. And yet only half, or slightly less than half, of the deaths that the coroner or medical examiner found it necessary to investigate were due to violence. Evidently still another group of cases demands attention. Deaths due to abortion, which are listed separately, may be disregarded because of their small number. There are left the deaths that the coroner or the medical examiner decides were due to natural causes. This group constituted from 42.5 to 69.4 per cent of all the deaths investigated, with an average of 50.5 per cent. These are the sudden deaths of persons who have not been attended by a physician. They must be investigated, because foul play must be excluded. Although the statutes of most states require that these deaths must be referred to the coroner, his authority does not appear to be well defined, and his main duty appears to be to exclude violence as a cause of death.

#### AUTHORITY OF THE CORONER IN NONVIOLENT DEATHS

It has already been noted that the authority of the coroner of Cook County has been limited by a ruling of the state's attorney's office. The effect of this limitation is evident from the figures for this jurisdiction in the accompanying table. It cannot be supposed that violent deaths are so much more numerous or sudden deaths so much less frequent

than in other localities as figures of 93.8 per cent for violent deaths and 5.1 per cent for deaths due to natural causes would appear to indicate.

The Illinois statutes that define the power of the coroner appear to make a positive presumption of violence a prerequisite for action by the coroner. The suddenness of the death and the possibility that the death was due to unlawful means are not enough. The investigation by the coroner of sudden, nonviolent deaths is in part the result of the inability of the physician to assign a cause for the death of a person whom he has not attended professionally. The coroner may act as the result of a provision embodied in the statutes of a number of states, requiring that the coroner be notified of such deaths.

Although the coroner's authority for the investigation of nonviolent deaths does not appear to be clearly defined by statute, the fact remains that he does act in these cases and that, except in Cook County, Ill., such deaths constitute half of the total number referred to the coroner's office. Granted that custom or law gives the coroner the right to act, at least to the extent of viewing the body, what is his authority in determining the cause of death? Is he to be held responsible for determining whether death was or was not due to violence or other unlawful means, and is he to be required to certify a cause of death if the latter was not due to violence or other unlawful means? He can do neither without a necropsy.

What, then, is the authority of the coroner to perform a necropsy if there is no positive suspicion of violence? The wording of the statutes of most states is such as to make the coroner's authority to hold an autopsy coequal with and dependent on his authority to hold an inquest. If he has no authority to hold an inquest, he appears to have no authority to order a necropsy. Many states have limited the coroner in the holding of inquests to cases in which death was presumably due to violence. His authority may be restricted even further by prohibiting the holding of an inquest if death was due to an accident. The law may limit the coroner still further by restricting him to the holding of an inquest only when there is a presumption that "death has been occasioned by the act of another by unlawful means" (criminal code of Alabama).

The letter of the law in most states would appear to place a definite curb on the activities of the coroner. In a number of instances<sup>8</sup> in

8. The following court decisions bearing on this point may be consulted: Palenzke v. Bruning, Branch Appellate Court, First District, Ill., 98 Ill. App., 644, 1900. Sandy v. Board of County Commissioners of Morgan County, Ind., Supreme Court, 87 N. E., 131, 1909. Coty v. Baughman, South Dakota Supreme Court, 210 N. W., 348, 1926. Streipe v. Liberty Mutual Insurance Company, Kentucky Court of Appeals, 47 S. W., (2nd) 1004, 1932.

which the spirit of the law has come before the higher courts for interpretation, the latter has in general been such as to uphold the letter of the law. Those who framed the laws relating to coroners in most of the states apparently had the inquest in mind as the most important function of this office. Court decisions interpret the coroner's necropsy as a part of the inquest that the coroner holds or is to hold.

Although the primary reason for requiring or permitting the coroner to investigate deaths that prove to be due to natural causes is to prevent the failure of detection of deaths that may have been brought about by unlawful means, the present organization of society presents still another important reason for referring to the coroner a group of sudden deaths that make up half of the cases referred to the coroner and approximately 10 per cent of all deaths occurring in a populous jurisdiction. The regulations of every civilized country make the filing of an official certificate of death the prerequisite for the legal disposal of the body. In the usual course of events, the death certificate is signed by the attending physician. If a physician is called for the first time to a person who is dying or has died, he cannot legally or honestly ascribe a cause of death. The duty of certifying the death then devolves on some agency of government. In most states, this agency is the coroner's office; it may be the bureau of vital statistics. If the local registrar is a layman, the cause of death as certified by him can be only the poorest sort of guess. If the deaths are referred to the coroner's office, the degree to which conditions are improved will depend on the thoroughness with which the coroner investigates such deaths. The failure of the coroner to determine accurately the cause of death in persons not attended by a physician may lead to serious vitiation of vital statistics. In 1926, 1927 and 1928, the number of death certificates originating in Cook County which were returned by the division of vital statistics of the federal census bureau as unsatisfactory because the cause of death was "ill-defined and unknown" was respectively eight, seven and nine. In 1929, when the coroner's activities were restricted by the legal advice of the state's attorney and by court injunction, the number of unsatisfactory death certificates increased to 104, and the indications in 1930 were that there would be a still further increase. This trend was contrary to what is happening in all other parts of the country.

It is evident that government has need of an agency that must assume the responsibility of certifying the cause of death in a not inconsiderable proportion of the total number of deaths. That agency should be the coroner's office, which has the authority to investigate violent deaths and determine their cause. It should also have the authority to make such examination as may be necessary to discover

the actual cause of death, when the latter is not due to violence and a probable cause is not evident to the physician.

The foregoing discussion of authority, as it relates to the determination of the cause of death when the latter is not due to violence, has been limited to the coroner. The authority of the medical examiner, who also must act in cases of sudden death, is more clearly defined by the laws that created the office.

#### PSYCHIATRY AND THE LAW

The need for some sort of medical service for the investigation of deaths of which society, as organized government, must take cognizance, was recognized in the early days of English law by the establishment of the office of coroner as a governmental agency. Another aspect of medical science, of ever increasing importance, has received less official recognition. Frequently called on in the past to help build up a defense of insanity, through which the perpetrator of a criminal offense might escape full responsibility for his act, psychiatry in the earlier days of the English law was of aid in the administration of criminal justice chiefly in distinguishing between the two extremes of stark, raving lunacy or complete imbecility, on the one hand, and complete sanity, on the other.

The advance of psychiatry during the past few decades has broadened the knowledge of mental reactions and behavior traits. The law has had to take cognizance of these advances by modifying the doctrine of right and wrong. It has recognized some of the lesser degrees of mental aberration that psychiatry has been able to delimit more precisely. But it has not accepted all the advances that psychiatry has made, because some of them are still the subject of debate and controversy. The administration of justice, in its attempt to evaluate these controversial matters, has been dependent on a contentious and partisan presentation of them. It does not have the advantage of impartial presentation of psychiatric fact and opinion to the extent that it has in respect to facts relating to the causes and circumstances of death through a governmental agency like the office of coroner or medical examiner.

Although there is in most states no established agency to which the courts may turn for unbiased opinion on psychiatric matters, Massachusetts, Baltimore and Cook County present examples of three different ways of arriving at the same end. Massachusetts laws providing for the psychiatric examination of certain classes of prisoners date back to 1849. A law passed in 1921 and amended in 1927 makes mandatory the psychiatric examination of all prisoners accused of a capital crime, and of all persons indicted for a felony who have been previously convicted of a felony or who have been previously indicted for any other

offense more than once. A law of 1924 extends psychiatric examination to convicted prisoners serving a sentence of more than thirty days in a jail or a house of correction and to prisoners in such institutions known to have served a previous sentence. The agency that makes these laws effective is the state department of mental diseases. The examinations are made by the personnel of the state hospitals, who act as the agents of the department of mental diseases, and who have available to them the services of the department's social workers and psychologists.

In 1920 the general assembly of Maryland passed an act creating the medical service of the Supreme Bench of Baltimore County. The primary function of this medical agency is to make psychiatric examinations of those persons who come within the jurisdiction of the Supreme Bench. The county commissioners of Cook County, Ill., on April 1, 1931, established the behavior clinic of the Criminal Court of Cook County.

These agencies have certain important features in common. Most fundamental of these is their purpose, that of furnishing to the courts advice on psychiatric matters. Since they, like the courts themselves, are supported by government, they furnish their advice without cost to the courts. Their cost is the cost of maintenance; their medical personnel receives no fees for the service rendered to the courts. The advice that they give is impartial and unbiased. They are not interested in the legal guilt or innocence of an accused person as is the psychiatrist who is retained by the defense or by the prosecution. Their chief concern is the proper disposal of those whose relation to a crime has been established.

These agencies also have some important points of difference. The system of psychiatric examination of prisoners in Massachusetts and the medical service of the Supreme Bench of Baltimore County have been established by legislative enactment. They may therefore be looked on as permanent, since legislative action would be necessary to discontinue them. The behavior clinic of the Criminal Court of Cook County was established by the action of a local governmental board. It may be discontinued at any time by the action of the board that established it. The Massachusetts system operates throughout the entire state. The activities of the other agencies are limited to local fields. Psychiatric examination of prisoners is mandatory and is a matter of routine under the Massachusetts system; it is made by the other agencies only when requested by the court or some other agency of government.

#### **EXPERT TESTIMONY AND THE HYPOTHETIC QUESTION**

The use of medical science in the administration of justice is hampered not only by the ineffectiveness that is inherent in the coroner

system or by the failure of the medical examiner system to make full use of medical science because of inadequate financial support or by the absence in most jurisdictions of an agency through which psychiatric opinion may be obtained, but also by the legal technicalities that surround the presentation of medical evidence. Knowledge that is beyond the ken of the average layman is presented in the form of expert testimony.

In civilized lands there are, in general, three ways in which facts or opinions relating to scientific or technical matters may be brought to the attention of courts and juries. The first of these makes the expert or a corps of experts a part of the tribunal. This method was formerly used occasionally in England, but has not been made use of in ordinary court proceedings in this country. In theory, this is an ideal method. In practice, it is not feasible because of the prohibitive cost of a corps of experts that might answer all questions that may come before a court.

Under the second method of procedure the court appoints a disinterested expert to act as adviser to the court or friend of the court. One difficulty with this method is that it places on the court the responsibility of determining the expertness of the court's adviser. Another difficulty relates to the legality or constitutionality of the procedure. Although many legal authorities seem to be agreed that the right of a court to appoint an impartial expert adviser is an inherent one under the common law, this right has been questioned by attorneys who have made the appointment of a court expert the basis of appeal.

The more recent trend of judicial opinion appears to uphold the right of a trial court to name its own experts. The courts, however, do not avail themselves of this privilege as a matter of routine. This may be because the means are not available for the employment of impartial experts. In those jurisdictions where the governmental machinery includes a psychiatric court service, the psychiatric expert serves the court as part of his official work.

The third method of presenting expert testimony, which is the one in most widespread use in the United States, has been termed by Maguire<sup>9</sup> the contentious or combative method. The expert is employed by the side retaining him. His fee is a private matter to be agreed on by his employer and himself. If the matter at issue is a controversial one, if it is one on which divergent opinions may honestly be held, the employer probably has the right to expect of his expert the opinion that will be advantageous to his contention. The hired expert, simply because he is hired, lays himself open to the suspicion of bias. Not infrequently this suspicion appears to be well founded.

9. Maguire, J. M.: *Expert Testimony*, Encyclopaedia of the Social Sciences, New York, The Macmillan Company, 1931, vol. 6, p. 13.

The contentious method of presenting expert testimony has bred a type of expert whose opinion appears to be purchasable. Maguire<sup>9</sup> referred to "the shallow competency of some experts whom the courts tolerate. . . . Now and then a notorious case stirs the suspicion that any man with a long enough purse can obtain expert testimony on either side of a question or on both sides successively."

The expert witness may have a firm and honest opinion and may be thoroughly honest and impartial in presenting it. But what Maguire has called "the ignorance, haggling and artificial restrictions with which lawyers and judges alike sometimes confuse presentation of specialized information" may place the honest expert in such a position that he is forced to contend for the correctness of his opinion. Having been forced into a combative and contentious attitude, he loses his value as an impartial expert. In Massachusetts and Baltimore, where the courts have the advantage of nonpartisan psychiatric opinion, the spectacle of two sets of experts belligerently opposing each other has almost completely disappeared. Partisan experts are rarely called, although both defense and prosecution retain their constitutional right to employ as many experts as they may desire.

The contentious method of presenting expert testimony operates under still another defect in addition to that which results from its contentiousness. All of the facts and contentions which have been admitted into the evidence, but which the expert has not himself heard or observed, may be combined into a hypothetic question which the expert is asked to answer. The hypothetic question is a legal technic the introduction of which had logic and reason as its basis. But the question has been subjected to such abuse, and its purposes have been so distorted as to defeat its original purpose. It is often so built up and contrived that its main function appears to be to confuse the court and the jury and to confound the honest witness. The latter may find the question itself a distortion of scientific facts, and the requirement that he express an opinion on it an insult to scientific intelligence.

The most severe criticisms of the hypothetic question as a legal technical procedure come, not from physicians who testify as experts, but from legal authorities. Of these, Wigmore<sup>10</sup> has gone so far as to propose that the hypothetic question be done away with entirely as a requirement for the presentation of expert testimony.

#### FOREIGN INSTITUTES OF LEGAL MEDICINE

In sharp contrast to the rôle of legal medicine in the administration of justice in this country is that of medical science in continental Europe.

10. Wigmore, J. H.: *A Treatise on the Anglo-American System of Evidence in Trials at Common Law*, ed. 2, Boston, Little, Brown & Company, 1923, sec. 686.

The practical application of medical science to the needs of justice occurs through the type of organization known as an institute of legal medicine. This is part of the governmental machinery, functioning under the department or ministry of justice. The medicolegal institute is also part of the university system, the director of the institute being also professor of legal medicine. As an agency of judicial administration the institute of legal medicine has the personnel, equipment and space that enable it to bring to bear on any investigation every resource of medical science. As a university department, the institute gives instruction to candidates for the medical degree, trains graduate students for careers in legal medicine, and prosecutes research in medicolegal problems.

In England, which uses the coroner system, there are no institutes of legal medicine. In Scotland, which uses the French system of preliminary investigation of crimes by a magisterial official known as a procurator-fiscal, the medicolegal institutes of the University of Edinburgh (founded in 1807), the University of Glasgow (1839), and Aberdeen University (1857) rank with the foremost of the continental institutes.

Functioning either as a part of the institute of legal medicine or as a separate unit in the local department of justice is the laboratory of police science. Such laboratories make use of the medical and other sciences in the detection of crime, the evaluation and preservation of circumstantial evidence, the apprehension of criminals and suspects and the identification of human beings. A description of some of the more important institutes of legal medicine will be found in the series of publications by the Rockefeller Foundation on the methods and problems of medical education.<sup>11</sup> A survey of the outstanding police laboratories and medicolegal institutes of Europe has been presented by Calvin Goddard,<sup>12</sup> managing director of the Scientific Crime Detection Laboratory of Chicago.

#### MEDICOLEGAL INSTITUTES IN THE UNITED STATES

Anything even remotely resembling the institutes of legal medicine of continental Europe, Scotland, Egypt, Japan and several South American countries exists nowhere in this country. The educational system and the methods of legal procedure in this country do not appear to lend themselves readily to the development of complete organizations like those of Europe. Even there, there is evident a tendency, according

11. *Institutes of Legal Medicine, Methods and Problems of Medical Education*, ser. 9, New York, the Rockefeller Foundation, Division of Medical Education, 1928.

12. Goddard, Calvin: *Am. J. Police Sc.* 1:13 and 125, 1930.

to Sand,<sup>13</sup> for "the vast subject of legal psychiatry . . . to isolate itself from legal medicine and to ally itself more closely to the general field of psychiatry."

Improvement in this country will probably occur most easily and most naturally along two distinct lines, which will not necessarily be consolidated into a single, complete institute of legal medicine. Development along the first of these lines will result in the more constant and thorough use of the laboratory medical sciences in the classes of deaths now investigated by coroners and medical examiners. The same service should be available for the investigation of nonfatal violence and injuries. Development along a second line will lead to governmental organizations through which impartial psychiatric service will be furnished to courts and other agencies of justice. Most states and larger municipalities already engage in a variety of scientific laboratory activities that might be expanded into a useful medicolegal service. The problem is not so much one of the creation of something entirely new as of the correlation and expansion of already existing agencies that might aid in the administration of justice by working for or through the office of coroner or medical examiner.

Although Morgan<sup>14</sup> has suggested that the duties and powers of the medical examiner be broadened to include a psychiatric service, the more logical development of medicolegal psychiatry would seem to be along the line of state-wide psychiatric examination of prisoners, as prevails in Massachusetts. Also, such a psychiatric service would not require the creation of an entirely new organization, but only the utilization of agencies that most states already have. Except in the largest municipalities or counties, where the volume of work may be great, the medicolegal institute and the psychiatric service should be state-wide in their functioning.

Scientific crime detection has great popular appeal, because of the spectacular character of some of its results. The state medicolegal institute could be so organized as to be able to render scientific aid in the detection of crime.

If one attempts to suggest a tentative coordination of scientific activities in such manner that medicine may further the administration of justice, it is not necessary to envisage a costly edifice with an organization entirely distinct from what may already exist. The purpose of

13. Sand, Knud: Origin, Development, and Status of Legal Medicine in Modern Times, Status of Legal Medicine in Denmark, and Description of Institute of Legal Medicine, Copenhagen, Institutes of Legal Medicine, Methods and Problems of Medical Education, ser. 9, New York, the Rockefeller Foundation, Division of Medical Education, 1928, p. 349.

14. Morgan, E. M.: Tr. Massachusetts Med.-Leg. Soc. 6:65, 1929.

the organization here proposed is merely to bring together the various medical activities that must receive consideration in any attempt to make medicine more useful to law, and to indicate the correlation of these activities along three main lines. Wherever possible such correlation should include the university as well as the agencies of government. A scheme of organization that would make medical science useful to law follows:

I. Division of Medical Laboratory Science. This division would act through, or for, the coroner or medical examiner and the public prosecutor. It must be staffed and equipped to be able to handle the work of the following departments:

1. Pathology
2. Bacteriology and Immunology
3. Toxicology and Chemistry
4. Records, Photographs, Museum, Roentgenography and Library

II. Division of Clinical Medical Science. This division would function in rendering unbiased expert opinion to prosecutors and to courts. It should be so organized that it could carry on the work of the following departments:

1. Psychiatry
2. Abnormal Psychology and Delinquency
3. Criminal Anthropology
4. Medical opinion in cases of nonfatal violence.

III. Division of Police Science. This division would function through or for the police agencies, including the municipal police force, the state constabulary, the prosecutor's office and the sheriff. It should consist of bureaus or departments for the following:

1. Police Administration. For the better organization and administration of police work.
2. Identification. For the utilization of every scientific procedure that has been found to be of value in the identification of criminal suspects, victims of crime or accident, and unknown persons.
3. Police School. For the training of the ordinary patrolman in his own duties, in the fundamentals of the work of the department as a whole, and in the essentials of the work of the police laboratory.
4. Police Laboratory. The police laboratory must be prepared to use, when necessary, the various medical and other sciences that may aid in the evaluation of clues and circumstantial evidence, and in the apprehension of suspects. It should train its own experts in those activities frequently required in the work of the police, and should have access to university faculty members or others expert in lines rarely needed in the usual work of the police department.

In the foregoing scheme, the division of medical laboratory science would constitute what would generally be thought of as the institute of legal medicine. The main element in the division of clinical medical science would be formed by such agencies as already exist or may be developed for the psychiatric examination of prisoners and those accused of crime. Some of the activities listed under this heading could be best carried on under university guidance. Most of the activities listed

under the division of police science should fall within larger police units, such as the state constabulary or the metropolitan police department. Such units should also have their own police laboratories for the carrying out of those technical procedures that could be performed by the trained personnel of the police unit. A police laboratory for more difficult and less frequently used procedures and for rendering service to the police agencies of less densely populated districts might well be included in the medicolegal institute contemplated in the first division proposed.

#### POSSIBILITIES FOR DEVELOPMENT OF LEGAL MEDICINE IN CERTAIN LOCALITIES

The evaluation of the present status of legal medicine in the United States has been based on a study of conditions in certain localities. Not the least important of the factors that influenced the choice of the localities selected was the need or the possibility for future development. Some of the most fundamental problems relating to the application of medical science to the needs of justice have been solved by the establishment of the medical examiner system. Those localities that have adopted this system offer the most promising field for further improvement.

Such criticisms as may be made of the offices of the medical examiners of New York City, Suffolk County (Boston), Mass., and Essex County (Newark), N. J., must be based on inadequate financial support of these agencies rather than on the character of the work done with the facilities available. These criticisms apply least to the office of chief medical examiner of Essex County, N. J., which renders to its community an almost ideal type of service. The relatively small area, the dense population and the excellent highway system of New Jersey would make this state an excellent testing ground for proving the value of a state-wide medical examiner system organized to meet the scientific needs of modern conditions. The medical examiner's office of Essex County could be easily expanded into a medicolegal institute that would serve the entire state as efficiently as it does its own community.

A relatively small increase in the annual budget of the office of chief medical examiner of New York City would enable this office to make more thorough application of scientific procedures in its work. The time of the chief medical examiner should be devoted largely to organization and administration and to the preparation of published work that would do much to advance the science of legal medicine throughout the United States. The large volume of work of this office would make it an important center for the training of those who wish to specialize in forensic medicine. The psychiatric clinic of the

Court of General Sessions, established in 1932, makes nonpartisan psychiatric service available to this court. Judges must be educated to make the widest possible use of such a service.

In Massachusetts, the routine psychiatric examination of prisoners and a state medical examiner system that has been in existence for fifty-five years form the foundation of what can be made the best state-wide medicolegal service in the country. Development of the procedures for psychiatric examinations will probably occur in the natural course of events, as the need for changes becomes manifest. The two medical examiner offices of Suffolk County should be combined into one. The large number of outlying medical examiner districts should be consolidated into a much smaller number in charge of full-time or half-time examiners. The medical examiner's office of Suffolk County, with an adequate personnel and with the quarters that are to be available in the new institute of pathology now under construction at the Boston City Hospital, should be the state medicolegal institute.

In jurisdictions using the coroner system, improvement will be less easy to bring about. Reform of the coroner's office by giving it better laws under which to operate and by providing it with a technical medical and legal staff not controlled or influenced by politics appears theoretically possible. The most desirable reform would be to replace the office of coroner by that of medical examiner. But that either degree of reform will occur in the near future appears unlikely. The best that can be hoped for is the establishment of medicolegal institutes to which coroner's offices can turn for guidance in scientific problems.

Development of such an institute in Chicago, in connection with the medical school of the state university, would result in an agency capable of rendering the highest type of scientific medicolegal service, not only to the coroner of Cook County, but to coroners throughout the state. The behavior clinic of the Criminal Court of Cook County and the psychiatric service of the Municipal Court of Chicago have proved their value and can be further developed as the need arises. The Scientific Crime Detection Laboratory, affiliated with Northwestern University, furnishes its services gratis to the police officials of Chicago and Cook County. In the case of Philadelphia not much is to be said, because there appears to be no great interest in local medicolegal problems.

Although the coroner's office in general presents some problems that appear to be rather hopeless of solution without a change in the character of the office, the coroner's office of Hamilton County (Cincinnati) Ohio, is an example of the improvement that can be brought about by coordination of effort. In 1931, at the suggestion of the newly elected coroner, the coroner's morgue in the county building was

closed and the morgue of the municipally supported Cincinnati General Hospital, which is part of the medical school of the city's university, was designated the coroner's morgue. The coroner appointed as his pathologist a pathologist recommended by the professor of pathology. The latter acts as unofficial consultant to the coroner's office. Proposed development of the university's department of psychiatry would correlate the work of this department with the needs of various community agencies, including the courts.

#### STATE UNIVERSITIES AND INSTITUTES OF LEGAL MEDICINE

The committee on medicolegal problems of the American Medical Association and the medicolegal committee of the section on criminal law of the American Bar Association have recommended the establishment in each state of a medicolegal institute so organized and equipped as to serve the needs of the entire state. In many of the states the state university would appear to be the logical and ideal seat of such an institute. Although the late Aldred S. Warthin, professor of pathology at the University of Michigan, had for many years urged the establishment of a centralized agency for medicolegal work at the university, the problems of legal medicine appear to have aroused little interest in the universities of states other than California.

The president of the University of California is keenly alive to the part that the university should play in the development of legal medicine. The university is situated in the populous San Francisco Bay area. Its southern branch at Los Angeles is in another densely populated district. Through its bureau of public administration, the university is in close contact with many state activities that could be coordinated into a medicolegal institute. A beginning in criminologic study and research has already been made through the recent organization of a department of police administration and the correlation of its work with that of the departments of psychiatry and criminal law. The fact that the coroner of San Francisco County is an appointive official, who serves for life or during good behavior, should simplify the bringing about of a liaison between the university and the coroner of that county.

#### MEDICAL ECONOMIC ASPECTS OF LEGAL MEDICINE

The thesis of this entire discussion is that legal medicine, if it is to serve society as efficiently as it should and if it is to undergo the development that should take place, is a function of government. It is frankly admitted that this conception raises some important medical economic problems. Group medicine, university hospitals, free and pay clinics, diagnostic clinics, forms of insurance that promise medical

care by physicians employed by the insuring company, and the medical care of war veterans are forms of practice that already seriously harass medicine as a profession. Back of them is the sinister shadow of state medicine. The thesis that the application of legal medicine is a function of the state requires justification.

No one will deny that the administration of criminal justice is a governmental function. The state must therefore have the inherent right to utilize every element that makes for competent administration. Of these elements, medicine is an important one. It is admittedly necessary in the work of the coroner or medical examiner, and it should be available in impartial form when psychiatric questions are involved. If the coroner does not have a technical staff capable of performing the medical duties of the office, he must employ private physicians when the necessity for this type of service arises. Under the usual system of obtaining psychiatric opinion, the courts must rely on physicians employed for the occasion, if funds for their employment are at hand. There are therefore two kinds of what may be termed professional medical experts, whose professional earnings will be influenced by the establishment of governmental agencies that would do away with the necessity for their services. These are the physicians who, either as individuals or as the proprietors of commercial laboratories, are employed from time to time by coroners, and the physicians who act as medical experts when psychiatric questions are involved. The rights of society as a whole must take precedence over the rights of individuals. Society, in the administration of criminal justice, is entitled to the best medical service obtainable, even if it jeopardizes the income of professional experts. The best medical service obtainable is to be had only through institutes of legal medicine administered by government and through psychiatric agencies such as the state has already set up for the study and care of the mentally unsound.

The establishment of impartial governmental medicolegal agencies does not interfere in any way with a defendant's right to employ experts of his own choosing. The fact remains, nevertheless, that in localities where nonpartisan psychiatric service is available few partisan experts are employed, and that in the medical examiner districts of New York City and Essex County, N. J., there is little medicolegal work for the commercial pathologist and the commercial laboratory. To this fact medicine will have to adjust itself in connection with the duty that it owes society in the administration of justice. It must be admitted that attempts to bring about a fuller realization of this duty of medicine to society will meet with the opposition of those who profit under the present incompetent system.

## LEGAL MEDICINE AS A UNIVERSITY DISCIPLINE

The discussion thus far has dealt almost exclusively with the practical application of medicine to the needs of justice. There is, as is evident from what has been said, much room and great need for the development of this aspect of legal medicine. But legal medicine, looked on as an important subdivision of medical science, cannot attain its fullest development unless it is made a field for teaching and research by the universities. The two aspects of legal medicine, the practical and the educational, are dependent on each other. Neither of them can go as far as it should without the other. Legal medicine as a science of practical application in the administration of justice needs the stimulus and guidance of legal medicine as a university discipline, and the latter needs the material and problems of the former for instruction and investigation.

In no university medical school of the United States is there a unified major department of forensic medicine in any way comparable with the teaching and research institutes of legal medicine of Europe. In the earlier study<sup>6</sup> of the offices of coroner and medical examiner, the statement was made (p. 83), based on investigation of the printed outlines of courses offered by the various medical schools of the country, that "in not a single school is there a course in which the student may be systematically instructed in those duties which he may be called upon to perform in connection with conditions which may arise as the result of crime or accident." This statement may be permitted to stand, although there have been some interesting developments in criminology and legal medicine in a few universities in the intervening period of four years. In the fall quarter of 1929, the newly created department of police administration of the University of Chicago offered graduate instruction in police administration to university students and a course in police procedure open to police officers. The head of that department resigned in 1931 to organize a similar department at the University of California, and under his guidance there has also been developed at the Junior College of San Jose, Calif., a two-year course of instruction in police work. The Scientific Crime Detection Laboratory of Chicago was organized in June, 1929, and began operation in April, 1930. It is affiliated with Northwestern University. A discussion of these recent university developments in criminology forms a supplement to bulletin 87<sup>1</sup> of the National Research Council.

Attention may be called to three developments in the field of legal medicine. Announcement was made early in 1932 of the appointment of Dr. George Burgess Magrath, for many years one of the two medical examiners of Suffolk County (Boston), Mass., to a professorship of

legal medicine in the school of medicine of Harvard University. This is the first endowed professorship of legal medicine in the United States. In the academic year 1931-1932, the medical school of the University of Illinois offered to senior medical students an optional course in legal medicine. This course was distinct from that in medical jurisprudence, which has been given for many years. A course in legal medicine, under the guidance of the chief medical examiner of New York City and the chief medical examiner of Essex County, N. J., is in the process of organization in the school of medicine of New York University.

The instructional work of a university department of legal medicine should be developed along two perhaps distinct lines. First would be the instruction of undergraduate students of medicine in the fundamental problems of legal medicine that they are apt to encounter in their professional work after graduation. Similar courses should be offered to the students of the university school of law. Second would be the training of graduates in medicine and law for careers in legal medicine. The postgraduate instruction should be correlated with research and investigation in those problems of forensic medicine that form such an important part of the work of foreign institutes of legal medicine.

#### SUMMARY

The present unsatisfactory status of legal medicine in the United States is the result of the American system of criminal judicial administration.

The basic medicolegal element in that system, in most jurisdictions, is the office of coroner. This office functions poorly. Its duties and authority are not clearly defined by law. It is an obscure elective office, whose incumbent as a rule needs to have no especial fitness for his position. Transplanted from England to the original colonies, the office has not been adapted to contemporary conditions and has become archaic.

Where provision is made for a technical staff for the coroner's office, that staff is hampered by the faults inherent in the office itself and by the failure to provide the staff with the facilities for scientific work.

In Massachusetts, in New York City, in Essex County, N. J., and in most of the New England states, the office of coroner has been replaced by that of medical examiner. The latter office functions much more satisfactorily than does that of coroner.

The chief criticism that may be made of the medical examiner system is that it fails to use to the fullest possible degree existing scientific medical procedures in its work. This is the result of inadequate financial support of the office.

A second factor that has retarded the progress of legal medicine is the failure of most jurisdictions to provide a means that makes unbiased psychiatric opinion fully and freely available to the agencies of justice.

Massachusetts, Baltimore County, Md., and Cook County, Ill., present examples of three different types of psychiatric court service. Similar or slightly modified agencies exist in some other localities, but on the whole psychiatry has not received the recognition in the administration of justice that its present position deserves.

The development of legal medicine has been further hampered by the contentious method of presenting expert medical testimony in use in most jurisdictions.

Improvement in the status of legal medicine and more efficient and more intelligent administration of justice require a more thorough application of medical science to law and justice than is the rule today.

Such fuller utilization of medicine is best brought about through the type of organization known as an institute of legal medicine.

The development of legal medicine in its practical applications will probably occur, if it does occur, along two lines: first, through agencies, which may be termed medicolegal institutes, that will function through or for the offices of coroner and medical examiner; and second, through agencies or procedures that will make impartial psychiatric opinion available to courts and other agencies of justice.

In a populous jurisdiction like that of New York City, the medicolegal institute should be a local institution developed from the office of medical examiner.

In Massachusetts and New Jersey, the present medical examiner offices of Suffolk County and Essex County, respectively, should be expanded into medicolegal institutes serving a state-wide examiner system.

In most states the medicolegal institute could be affiliated with, or could be part of, the state university.

Both the medicolegal institute and the psychiatric court service can probably be developed from activities already being conducted by the state.

If the office of coroner is to participate as fully as it should in the application of medicine to justice, reform of this office is desirable.

The administration of justice is a function of government. As such it is entitled to the highest type of impartial service that medicine can give.

The development of legal medicine as a science of practical application should go hand in hand with the development of forensic medicine as a university discipline.

## Notes and News

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**University News, Promotions, Resignations, Appointments, Etc.**—Louis C. Kress of the State Institute for the Study of Malignant Disease, Buffalo, has been appointed assistant director of the division of cancer control of the New York State Department of Health.

George K. Mallory has been appointed instructor in pathology in Harvard Medical School, Boston.

James A. Doull, professor of hygiene and public health in Western Reserve University, will organize a comprehensive epidemiologic study in the Philippine Islands under the auspices of the Leonard Wood Memorial for the Eradication of Leprosy.

At Columbia University Richard Thompson has been appointed assistant professor of bacteriology.

Charles Norris has been appointed professor, Harrison Martland associate professor, and Armin V. St. George assistant professor in the new department of forensic medicine just established in the University and Bellevue Hospital Medical College, New York.

**Society News.**—The Pathological Society of Philadelphia celebrated its seventy-fifth anniversary on March 9, 1933.

**A New Medicolegal Journal.**—The Medico-Legal Society in London has commenced the publication of a new journal, the Medico-Legal and Criminologic Review, which will appear quarterly under the editorship of Gerald Slot and Everard Dickson. In addition to original articles and reports of medicolegal societies, the new journal will contain an extensive abstract department with sections as follow: criminal and social prophylaxis; medicolegal aspects of drunkenness; forensic obstetrics; forensic psychiatry and psychology; injuries; insurance medicine; occupational diseases; paternity and blood grouping; poisoning; therapeutic accidents and medical negligence; violent death from physical causes. The publishers are Baillière, Tindall and Cox, Henrietta Street, London, W.C.2. The annual subscription price is \$3. This journal promises to meet needs for an English periodical dealing with medicolegal matters.

## Abstracts from Current Literature

### Experimental Pathology and Pathologic Physiology

EFFECT OF ROENTGEN IRRADIATION ON THE KIDNEY. R. ENGER and P. PREUSCHOFF, *Virchows Arch. f. path. Anat.* **283**:489, 1932.

The literature relating to the action of roentgen rays on the kidney is reviewed. Considerable discrepancy of observation exists as to whether the chief damage is to the arteries, the glomeruli or the tubules. In the experiments reported here, four male dogs were subjected to repeated mild irradiation of the renal region. The dosage of each exposure was from 60 to 140 per cent of the human skin erythema dose, and the exposure was repeated at intervals of from eight days to three months over a period of from five months to one and a quarter years. The total dosage was from 5.8 to 21 human skin erythema doses. Eight days after each irradiation the animals were isolated in metabolism cages over five day periods for chemical studies. The earliest change noted was a decrease in the excretion of urochrome. Urorrhodin was increased in the urine and could be detected in the blood. Urea and nonprotein nitrogen increased progressively in the blood, reaching values from two to four times the original determinations, depending on the length of the experiment. The indican and xanthoprotein of the blood increased. The blood pressure was permanently elevated in two of the animals. The urine contained only traces of albumin. Examination at the conclusion of the experiments revealed a decrease in the size of the kidneys. In two of the animals, one kidney was reduced to a greater degree than its mate. This is ascribed to unavoidable differences in the irradiation of the two sides. The chief damage was to the tubules, the epithelium of which exhibited various kinds and varying degrees of degenerative change. The glomeruli and blood vessels were practically unaffected.

O. T. SCHULTZ.

A REVIEW OF THE LITERATURE ON THE SPECIAL PHYSIOLOGY OF THE KIDNEY. GÖSTA EKEHORN, *Virchows Arch. f. path. Anat.* **283**:664, 1932.

The issue preceding that in which this article by Ekehorn appears contained (p. 434) a lengthy article (which was not abstracted for the ARCHIVES) in which he expressed the belief that research on the pathologic anatomy and physiology of the kidney had come to a standstill because such research dealt largely with the application of the facts of general physiology to the kidney, and did not sufficiently take into consideration the special physiology of the kidney. New lines that research should follow were discussed. The present communication is a review and critical discussion of the literature relating to the special physiology of the kidney as a whole.

O. T. SCHULTZ.

EXPERIMENTAL FIBROUS OSTEODYSTROPHY IN THE DOG WITH PSEUDOTUMORS AND CYSTS OF THE JAW. M. WEBER and H. BECKS, *Virchows Arch. f. path. Anat.* **283**:752, 1932.

Accepting Christeller's terminology of osteodystrophia fibrosa for a group of diseases of the osseous system that includes osteitis deformans (Paget's disease), generalized osteitis fibrosa (von Recklinghausen's disease) and localized osteitis fibrosa, the authors report the experimental production of osteitis fibrosa in dogs. At the age of about 6 weeks the animals were placed on a standard purified diet that was poor in calcium and contained no vitamin D. Four animals maintained on the diet for from three to eight and one-half months revealed generalized osteitis fibrosa. In the jaw there were cysts and hemorrhagic giant cell granulomas,

so-called "brown tumors," which are termed by the authors intra-osseous epulides. Histologically, bone lesions were identical with those of human osteitis fibrosa and were not to be confused with those of rickets or with those of osteoporosis. In one animal that died of an intercurrent disease there had developed osteitis fibrosa of the pseudo-osteomalacia type, but without tumors or cysts of the jaw. In a second animal that died of intercurrent disease, generalized osteoporosis developed. In these two animals, as compared with the four in which the typical disease was produced, the intercurrent disease is believed to have interfered with bone formation.

O. T. SCHULTZ.

**DYNAMICS OF CARDIAC HYPERTROPHY AND DILATATION.** A. PODKAMINSKY, *Virchows Arch. f. path. Anat.* **284**:92, 1932.

Anatomically and functionally there can be recognized in the muscular wall of each ventricle of the heart a portion that is related to the path of inflow and another that is related to the path of outflow. The function of the former is to furnish the force for driving the column of blood forward. The wall of the path of outflow directs the blood into the pulmonary artery or into the aorta. Increased tension of the heart muscle causes primarily hypertrophy of the muscle of the path of inflow and dilatation of the wall of the path of outflow, since the latter receives the first impact of the moving column of blood. Enlargement of the heart in its initial stages is therefore not due entirely to either hypertrophy or dilatation, but is a complex of hypertrophy of one part of the wall and dilatation of another. Continuation of the factor that initiates the process later leads to hypertrophy of the primarily dilated portion and to dilatation of the part primarily hypertrophied. Ultimately dilatation of the entire chamber may occur. The roentgenographic evidences of partial hypertrophy and dilatation are described.

O. T. SCHULTZ.

**EXPERIMENTAL ARTERIOSCLEROSIS.** E. PFLEIDERER, *Virchows Arch. f. path. Anat.* **284**:154, 1932.

This is a continuation of some previous work of Schmidtmann, under whose direction these experiments were carried out. Schmidtmann had found that the administration of both cholesterol and viosterol (vigantol) caused a greater degree of arterial involvement than did that of cholesterol alone, and that the resulting changes were more like those of human arteriosclerosis. The experimental conditions were varied in a number of ways. Young and fully grown rabbits were used; the two substances were given simultaneously over varying periods of time; they were administered separately, with varying periods of time intervening; the dosages were varied, but the dose of each substance was always less than that known to be necessary to cause the changes characteristic of the substance. Adult rabbits were more susceptible than young ones. The most marked changes resulted when very small doses of viosterol were administered for a short period of time, followed by the administration of cholesterol after a long interval. The changes caused by the viosterol, which are progressive and continue for a considerable time after the cessation of administration, render the damaged arterial wall more sensitive to cholesterol. The resulting alteration, in the character of the aortic lesions and in the involvement of peripheral arteries, especially the coronary and renal arteries, is more similar to human arteriosclerosis than is the atheromatosis due to cholesterol alone. In experiments on rats, if the functional activity of the arterial system was increased, as by exercising the animals in a treadmill, it was found that the degree of arterial damage was greater than in rats that were not exercised, and that coronary arteriosclerosis resulted regularly. The action of viosterol in rendering the arterial wall more sensitive to cholesterol is not specific for viosterol; in rats, it was found that epinephrine, which also damages the media, similarly rendered the artery more susceptible to cholesterol when the latter was administered after an interval.

O. T. SCHULTZ.

**EFFECT OF DIURETICS ON THE OUTPUT OF WATER BY THE SKIN.** J. K. MAYR,  
Virchows Arch. f. path. Anat. **284**:354, 1932.

In normal subjects, the diuresis caused by increased intake of water was found to be associated with a moderate increase in the quantity of water excreted by the skin. In subjects with generalized disease of the skin and with normal renal function, the output of water by the skin, under controlled conditions, was greater than in subjects with normal skin. In those with skin diseases and with an increased basal level of water excreted by the skin, the diuresis caused by increased intake of water was delayed six hours or longer, whereas the output of water by the skin was greatly increased. Under similar conditions caffeine had the same effect. Theobromine had no appreciable effect on the excretion of water by the normal kidney or by the diseased skin. Euphyllin caused an increase in both urinary and cutaneous excretion, the latter persisting longer than the former. The results after administration of salyrgan and merbaphen were not uniform: in some instances, the excretion of urine by the normal kidney was increased; in others, cutaneous perspiration was increased. Potassium acetate had no effect on the excretion of water by the normal skin. But in skin diseases with increased basal output of water, potassium acetate caused a great increase in cutaneous excretion, with a correspondingly decreased diuresis. In generalized skin diseases, the water metabolism is altered, but not always in the same manner or to the same degree, as judged by the varying effects of the diuretic agents studied.

O. T. SCHULTZ.

**Pathologic Anatomy****INTRACRANIAL INCLUSIONS IN HUMAN NERVE CELLS IN A VARIETY OF DISEASES.**  
A. WOLF and S. T. ORTON, Bull. Neurol. Inst., New York **2**:194, 1932.

We are recording the finding of intranuclear bodies in the nerve cells of persons who died from a wide variety of diseases. These masses are similar in appearance and in staining reaction to the descriptions and illustrations of others who have interpreted them as specific intranuclear inclusions associated with diseases caused by filtrable viruses. Three possible explanations of the range and frequency of our findings are suggestive: (1) that the intranuclear bodies are nonspecific products of degeneration of the nucleoplasm; (2) that the human nervous system may frequently harbor a latent virus capable of giving rise to intranuclear inclusions without producing a characteristic disease, and (3) that the specific inclusions resulting from virus diseases cannot be differentiated with security from nonspecific degeneration products.

AUTHORS' SUMMARY.

**HISTOLOGIC STUDIES ON HOG CHOLERA.** O. SEIFRIED and C. B. CAIN, J. Exper. Med. **56**:345 and 351, 1932.

In cases of acute hog cholera the earliest and most pronounced lesions occur in the capillaries and smaller arteries. Larger arteries and veins are less frequently involved. The lesions consist of swelling and proliferation of endothelial cells together with retrogressive changes in them and in the other parts of the blood vessel walls. The character and degree of these lesions seem to be dependent on the virulence of the virus and, to some extent, on the presence of secondarily invading bacteria. We believe that these lesions should be considered a principal feature of the histopathologic picture of hog cholera.

The hemorrhages, foci of necrosis and anemic infarcts in the various organs in virus hog cholera result primarily from the vascular lesions described in a previous paper of this series. Although they are not dependent on the presence of secondarily invading bacteria, their severity is influenced by these organisms. The lesions in the lymph nodes, spleen, kidneys and central nervous system seem to be of special diagnostic value in questionable cases of hog cholera. The presence of encephalitis alone does not justify the diagnosis of hog cholera because in the central nervous system of swine similar inflammatory lesions occur in other diseases.

AUTHORS' SUMMARY.

**SIGNIFICANCE OF RETICULUM FIBERS IN PULMONARY TUBERCULOSIS.** S. PUDER, Beitr. z. Klin. d. Tuberk. **80**:229, 1932.

The reticulum fibers are important constituents of tuberculous tissue. They originate from epithelioid cells. They are resistant to necrosis and are frequently well preserved in caseated foci. They may grow into caseated foci in the neighborhood.

MAX PINNER.

**HISTOLOGY OF THE HEART IN EXOPHTHALMIC GOITER.** H. BAUST, Beitr. z. path. Anat. u. z. allg. Path. **86**:543, 1931.

The histologic changes in exophthalmic goiter consist of a slight increase in the interstitial and perivascular lymphocytes, histiocytes and fibroblasts, localized in the outflow tract of both chambers. Parenchymatous degenerative changes, scarring and actual inflammatory changes were not found. In colloid goiter, nodose goiter and Riedl's struma changes were absent.

W. S. BOIKAN.

**SKELETAL CONDITIONS IN CRANIORACHISCHISIS.** A. MATERNA, Centralbl. f. allg. Path. u. path. Anat. **54**:1, 1932.

Materna studied the angle of kinking in the cervical region in various grades of craniorachischisis and is convinced that the backward bending of the cervical vertebrae is an argument in favor of the pressure theory of origin of this anomaly. The degree of such kinking determines the exterior aspects of the body. In acute angled kinks the ears lie on the shoulders, because there is no neck. In a right-angled kink the neck is short. The presentation of the face in such bodies is also determined by the cervical angulation. Thus in a right-angled deformity the face presents forward and upward at an angle of 45 or more degrees posterior to the normal vertical. In acute cervical angulation the face is at a right angle to the vertical axis.

GEORGE RUKSTINAT.

**FATAL FIBROSIS OF THE LUNGS DUE TO INHALATION OF RADIUM.** Clinical Part, F. DOENECKE; Pathologic Anatomic Part, J. H. BELT, Frankfurt. Ztschr. f. Path. **42**:161 and 170, 1931.

A 35 year old chemist whose occupation was the extraction of mesothorium and radiothorium from ore residues complained of difficulty in breathing for two years. On his first admission, the diagnosis of possible chronic bronchitis was made. At that time examination of the blood revealed 5,400,000 erythrocytes and 6,300 white blood corpuscles. At the second examination, six months later, the heart was enlarged and the roentgenogram revealed small nodular areas throughout the lungs. During his stay in the hospital he had several attacks of severe dyspnea. The sternum during these attacks seemed to be firmly attached to the mediastinum and to follow closely the inspiratory movements of the chest. A short time before death the temperature rose to 39.2 C. (102.6 F.), and the patient experienced a chill. He gradually became cyanotic, the pulse became weaker, and death occurred twenty-five days after the second admission to the hospital. No definite diagnosis could be made clinically.

Autopsy revealed a marked fibrosis of almost all portions of the lungs. There were scars in both upper lobes and in the right middle and upper portions of both lower lobes. The lungs had a combined weight of 930 Gm. and were brownish red and of rubbery consistency. Also, acute fibrinous pleuritis was noted. The heart, especially the right ventricle, was dilated; it weighed 350 Gm. There was edema of the brain. Otherwise no marked changes were noted at autopsy. Histologic examination of the lungs revealed marked thickening of the interlobar septums and coarse fibrous alveolar walls. The fibrous tissue was poor in nuclei and contained many coarse elastic fibers and a few blood vessels. There were no nodules and no evidence of tuberculosis or of chronic bronchitis. The alveolar lining cells were thin and atrophic and in places could not be made out. Many

heart failure cells were also present in some fields. The lower lobes also revealed acute bronchopneumonia. In these sections there also were many hyaline-like rings lining the inner portions of some of the alveoli and ducti alveolares.

The various possibilities which may lead to such a diffuse fibrosis of the lungs are discussed. Even though there is no absolute proof that inhalation of radium had caused the changes in the lungs, there is, however, in all probability, a relation between the damage caused by the radium and death resulting from fibrosis of the lungs.

O. SAPHIR.

**THE ENLARGEMENT OF THE AORTIC VALVE IN SYPHILITIC AORTITIS.** P. RADNAI, Frankfurt. *Ztschr. f. Path.* **42**:228, 1931.

In diseases of the ascending aorta, especially in cases of syphilitic aortitis, the cusps of the aortic valve become larger provided that the syphilitic process does not extend into the valves themselves. The aortic cusps are much wider than the mouth of the aorta itself. No definite explanation for these findings is given, but possible causes are discussed, such as a decreased elasticity of the aorta and an increased pressure on the aortic valve during diastole.

O. SAPHIR.

**MALFORMATION OF THE SKULL IN CASES SHOWING A NASO-ORBITAL ENCEPHALOCELE.** H. MUSSGNUG, Frankfurt. *Ztschr. f. Path.* **42**:238, 1931.

Two cases are reported. In the first instance there was a defect of the skull involving the left frontal bone, and the ethmoid, right nasal and maxillary bones. The left lacrimal bone was entirely missing. In the second instance, the involved bones were the ethmoid, maxillary, nasal and lacrimal. The author believes that both conditions, the malformation of the skull and encephalocele, were the result of one common cause, probably the effect of an outside force directed on the anlage of the skull early in the development of the fetus.

O. SAPHIR.

**STRUCTURE OF TEETH IN CASES OF EXTENSIVE SKELETAL CHANGES.** N. ZAJEW-LOSCHIN and S. J. LIBIN, Frankfurt. *Ztschr. f. Path.* **42**:245, 1932.

Ten cases which revealed changes in the bones and also caries of the teeth were examined. In all these cases there was a decrease of the calcium content of the bones. The author believes not only that lack of calcium plays an important rôle in the causation of caries of the teeth, but that exogenous factors must be taken into consideration.

O. SAPHIR.

**PATHOGENESIS AND MORPHOLOGY OF SYRINGOMYELIA.** K. J. HOFFMANN, Frankfurt. *Ztschr. f. Path.* **42**:261, 1931.

Seven cases are reported. In four of these a primary gliosis with formation of the cavities was encountered. In the three remaining cases there were primary tumors of the spinal cord combined with gliosis. The author believes that the gliosis is the result of a developmental disturbance in the fetus. The glia proliferates, predominantly within the gray substance; the central canal may be obliterated or dilated, or may not be at all demonstrable. The primary gliosis may predispose to the formation of glioma. In several instances, circulatory disturbances were found within the spinal cord. Such changes may be of significance in explaining the progressive gliosis and formation of cavities.

O. SAPHIR.

**CHANGES IN THE EXTRAHEPATIC BILE DUCTS WITH AGE.** J. F. NUBOER, Frankfurt. *Ztschr. f. Path.* **42**:292, 1931.

While in children the gallbladder in general appears cylindric, in the adult it is pear-shaped. The ductus hepatocholedochus becomes wider with increasing age. Its form, however, shows little change. Also, the cystic duct increases in

width but not as regularly as the ductus hepatocholedochus. Histologically, there are more elastic fibers and distinctly hypertrophic muscle fibers in the gallbladder in older persons. The ductus hepaticus and ductus choledochus also reveal more elastic fibers with increasing age. The increase of elastic fibers within the cystic duct, however, is less marked.

O. SAPHIR.

**AGNESEA OF THE GALLBLADDER.** F. BARNSDORF, Frankfurt. *Ztschr. f. Path.* **42**:304, 1931.

The literature on agnesia of the gallbladder is reviewed, and one new case is reported. The absence of the gallbladder was an incidental finding. The lower surface of the liver, where the gallbladder is situated under normal conditions, was perfectly smooth. The author concluded that agnesia of the gallbladder is clinically without significance.

O. SAPHIR.

**RELATIONS BETWEEN SYPHILITIC AORTITIS AND ATHEROSCLEROSIS.** R. NEUMANN, Frankfurt. *Ztschr. f. Path.* **42**:319, 1931.

The clinical diagnosis in the case of a 19 year old youth was ulcerating endocarditis with metastatic pyemic abscesses in the skin and lungs. Osteomyelitis of the right humerus was thought to be the cause of the pyemia. At autopsy, abscesses were found in the myocardium, lungs, spleen, kidneys, meninges and skin. There was also acute osteomyelitis of the right humerus. The aorta showed a series of changes. There were acute inflammatory changes in the adventitia, which also extended into the media. Small vessels were plugged with emboli consisting of staphylococci. In addition to these lesions, there was grossly and histologically typical syphilitic aortitis with involvement of the aortic valve. The intima revealed hyperplastic and degenerative changes. Because of the marked intimal thickenings and because of the extensive regressive changes found in the intima, the author believes that the intimal changes are atherosclerotic in nature rather than a reaction to the syphilitic process in the media. However, the staphylococcal infection and the syphilitic aortitis might have been predisposing factors for the development of the arteriosclerosis.

O. SAPHIR.

**TRAUMATIC DESTRUCTION OF THE CORPUS CALLOSUM WITHOUT FRACTURE OF THE SKULL.** J. KARSCH, Frankfurt. *Ztschr. f. Path.* **42**:375, 1932.

A man, 36 years old, was thrown from a motorcycle and died about thirty-seven hours after admission to the hospital. At autopsy, the corpus callosum in its posterior portion was completely destroyed, while its anterior portion was torn in several places. A moderate amount of blood was found in the third and lateral ventricles. The dura and the skull were intact. Some blood was present in the subdural space. The author also reviews the literature and concludes that severe trauma to the head does not necessarily lead to fracture of the skull, but may cause a rupture of the brain.

O. SAPHIR.

**THE VARIATIONS IN THE DISTRIBUTION OF THE ELASTIC FIBERS IN THE HUMAN SKIN.** E. LINDHOLM, Frankfurt. *Ztschr. f. Path.* **42**:394, 1932.

The corium of the human skin was the field of the investigation. The following conclusions are reached: The elastic fibers in infants of both sexes are, as a rule, more numerous than those found in adults. In females the number of elastic fibers is often larger than that in males. However, the smallest number of elastic fibers found at any age was in the female. The male infants showed fewer elastic fibers in the skin covering the abdomen than in the skin corresponding to the thorax. Among adults, the majority of women revealed more elastic fibers in the abdominal skin than in the thoracic skin. This is of significance because of the importance of the elasticity of this part of the skin during pregnancy. In

men, the number of fibers in the abdominal skin most commonly was less than that in the thoracic skin. The author expresses the belief that the individual variation of the elastic fibers often present at birth is of importance in considering the physiologic and pathologic conditions of the person, and tries to correlate the variation in the distribution of the elastic fibers with the constitution of the subject.

O. SAPHIR.

**INNER AND MIDDLE EAR IN CASES OF MALFORMATIONS OF BRAIN AND SKULL.**  
B. G. TURKEWITSCH, Frankfurt. *Ztschr. f. Path.* **42**:415, 1932.

In a detailed article, the author points out certain correlations between the structures of the labyrinth and the brain. He believes that according to structural changes it may be possible to determine the time of the interruption of the normal development of the brain in cases of anomalies of the brain. Also, the changes in the brain per se may lead to certain conclusions as to what changes may be expected in the labyrinth. The author recommends experimental animal research by destruction of the brain in a very early period of the development and simultaneous investigation of the labyrinth in these instances.

O. SAPHIR.

**LYMPHOGRANULOMATOSIS OF THE SPINAL COLUMN.** E. TETZNER, Frankfurt. *Ztschr. f. Path.* **42**:545, 1932.

The literature is reviewed, and eight new cases of lymphogranulomatosis are added. Among the patients there were five men and three women. The ages varied from 24 to 50. In all cases, with the exception of one, changes in the spinal column were found. The changes in the bone consisted, as a rule, in replacement of portions of the bone marrow by typical lymphogranulomatous tissue. Three cases also showed lesions of the femur. Another case revealed typical changes in the skull in addition to changes in the spinal column.

O. SAPHIR.

**DESQUAMATION OF CELLS OF FOLLICULAR LINING IN EXOPHTHALMIC GOITER.**  
K. KUROKAWA, Frankfurt. *Ztschr. f. Path.* **43**:36, 1932.

The author examined portions of the thyroid removed at operation from a patient suffering from exophthalmic goiter. As the patient died a few hours after the operation, the remainder of the thyroid was secured for examination two hours after death. While the specimen removed before death showed no desquamation of the cells lining the follicles, the portion removed at autopsy showed many desquamated cells. Several authors are quoted who state that desquamation of epithelial cells in the thyroid in cases of exophthalmic goiter is one of the characteristic histologic features, but Kurokawa concludes that such desquamation does not occur during life, being only a postmortem phenomenon.

O. SAPHIR.

**Microbiology and Parasitology**

**DIPHTHEROID BACILLUS AND STREPTOCOCCUS IN ACUTE ENDOCARDITIS.** A. T. and H. F. WECHSLER, Am. J. Dis. Child. **44**:156, 1932.

Clinically and pathologically the case reported was one of acute vegetative endocarditis of the mitral valve, complicated by widespread embolic phenomena. The interesting feature was the isolation of a pure culture of a diphtheroid bacillus from the blood stream seven and two days before death and from the heart's blood at autopsy. Repeated blood cultures up to that time had yielded negative results. We were therefore greatly surprised when smears of the vegetations showed the presence of a streptococcus in association with the diphtheroid bacillus. That in a small number of cases of acute endocarditis, usually estimated at 10 per cent, the streptococcus cannot be recovered from the blood stream is well known. Besides these considerations, the extreme rarity, if not altogether doubtful existence,

of a diphtheroid endocarditis makes it highly probable that the streptococcus was the etiologic organism in our case and the diphtheroid bacillus a secondary invader.

#### AUTHORS' SUMMARY.

**EXPERIMENTAL STUDIES ON MALARIA OF MONKEYS.** WILLIAM H. TALIAFERRO, Am. J. Hyg. **16**:429, 1932.

Histologic studies were made of tissues from monkeys infected with malaria. The most marked histologic changes were found in the liver and spleen, where there was an evident increase in numbers and of phagocytic activity of the differentiated macrophages and a general activation of the more primitive lymphoid tissue.

RALPH FULLER.

**BRUCELLA MENINGO-ENCEPHALITIS WITH MYCOTIC ANEURYSM.** G. H. HANS-MANN and J. R. SCHENKEN, Am. J. Path. **8**:435, 1932.

The article reports a case of meningo-encephalitis in a man, 24 years old, due to *Brucella melitensis* of the porcine variety. The immediate cause of death was the rupture of a mycotic aneurysm.

**THE PATHOLOGY OF AMEBIASIS IN CARRIERS.** CHARLES F. CRAIG, Am. J. Trop. Med. **12**:285, 1932.

The author concludes from the evidence of his animal experiments and from his postmortem observations in carriers of *Endamoeba histolytica*, that there is no support for the theory that this organism can live in the intestine indefinitely without producing lesions. Strictly speaking, there is no such thing as a "healthy" carrier of *Endamoeba histolytica*, if by that term is meant one in whom lesions caused by the parasite are not produced, and it is doubtful if the term "carrier" should be used at all with reference to infection with this parasite. So-called "carriers" are very resistant to the amebic infection, and the minute superficial lesions are quickly healed, but when the resistance is lowered from any cause, the lesions progress, and the symptoms of the infection will appear sooner or later. In every person harboring the parasite, it is a potential source of injury to the tissues and health of the host, and as soon as the infection is discovered appropriate treatment should be instituted at once, whether symptoms are present or absent.

S. W. MENDELSON.

**SPONTANEOUS SPIROCHETOSIS AND EXPERIMENTAL SYPHILIS IN RABBITS.** S. M. FRIED and S. S. ORLOV, Arch. Dermat. & Syph. **25**:893, 1932.

Spontaneous spirochetosis is an autonomous disease found in rabbits (and probably in the field hare). The infection caused by *Spirochaeta cuniculi* is transmitted from animal to animal by genital contact only, leading to a chronic disease of the skin in the anogenital region (and, in females, of the mucosa) and sometimes also of other parts of the body. The process is sometimes accompanied by a regional adenopathy. The occasional presence of spirochetes in the tributary lymph nodes and also in the blood reported by some authors was not confirmed in these studies. The Wassermann and the Sachs-Georgi reactions are, as a rule, negative in spontaneous spirochetosis. Animals cured of spontaneous spirochetosis are susceptible to new infections. *Spirochaeta cuniculi* causes no specific lesions in the viscera or in the central nervous system. Likewise the cerebrospinal fluid in this disease shows no cytologic or chemical changes. Spontaneous spirochetosis is a local parasitic disease of the skin which may be generalized in rare instances. It is believed that in spite of the morphologic identity of *Spirochaeta cuniculi* and *Spirochaeta pallida*, their biologic properties and the processes that they cause are entirely different. The two diseases can be differentiated by clinical and laboratory tests. In difficult cases the therapeutic test with bismuth or arsphenamine may be a reliable guide in the differential diagnosis. This study has revealed (as others also have observed) that, not infrequently, apparently normal rabbits

show changes of the viscera, central nervous system and cerebrospinal fluid which resemble those seen in advanced syphilis in man. The results obtained from the study of the syphilitic disease of these organs in the rabbit must, therefore, be accepted with reservations.

#### AUTHORS' SUMMARY.

#### PSITTACOSIS WITH RESULTS OF POSTMORTEM EXAMINATION IN A CASE INCLUDING STUDIES OF THE SPINAL CORD. S. H. POLAYES and M. LEDERER, Arch. Int. Med. 49:253, 1932.

The report deals with a household epidemic of psittacosis in which five people were afflicted with the disease carried by sick parrots. The postmortem examination was of the body of a 51 year old woman from whose lung, liver and spleen G. P. Berry isolated the virus of psittacosis. This was also isolated from the sputum of one of the survivors in the family and from the liver and spleen of one remaining parrot. In the body examined there was edema of the submucosa of the larynx, trachea and bronchi. Microscopically these places contained mononuclear, plasma and occasional polymorphonuclear neutrophilic cells. A thick layer of fibrin separated the zone of infiltration from the stroma beneath. Some differential points between psittacosis and influenza are stressed, as regards the pulmonary lesions. The changes in the spinal cord were definite but not characteristic, since similar changes may occur in other toxic states. The changes consisted of moderate chromatolysis of the anterior horn cells and an increase in glia cells. Some of the neurons showed a transformation of the usual pyramidal form into rounded or otherwise distorted shapes and an eccentric position of the nuclei.

GEORGE RUKSTINAT.

#### SYSTEMATIC BLASTOMYCOSIS. T. S. RAIFORD, Bull. Johns Hopkins Hosp. 51:61, 1932.

A case of systemic blastomycosis with primary involvement of the skeletal system is herewith reported. The interesting features of the case are the widespread involvement of the bones, the absence of typical concomitant lesions and the response to treatment with various drugs. The literature is briefly reviewed, and although many cases of blastomycosis have been reported, none was found bearing a distribution similar to that present in this case. Although the bones are frequently the seat of the lesion, the majority of cases likewise show involvement of other organs. The pathologic lesions are similar to those of tuberculosis and chronic osteomyelitis of the bone, with a marked degree of osteolysis and minimal new bone formation. The three conditions are frequently confused. The clinical features resemble those of any generalized infection, and the nature of the disease is proved only by finding the organisms in the pus from the sinuses or in biopsy specimens from the soft tissue. Prognosis is uniformly poor, and advanced cases almost invariably terminate fatally. The treatment consists of proper hygienic measures, supplemented by certain types of drugs, among which potassium iodide, ethyl iodide and gentian violet are most efficacious.

AUTHOR'S SUMMARY.

#### BRUCELLA ABORTUS IN THE TONSILS. C. M. CARPENTER and RUTH A. BOAK, J. A. M. A. 99:296, 1932.

The isolation of *Brucella abortus* from the tonsils in eight of sixty-four cases is reported. Most of the persons concerned had been drinking raw milk known to contain *Brucella abortus*. Except in one case, there was no evidence of undulant fever in these persons.

#### ACTINOBACILLUS BACTEREMIA. L. THOMPSON and F. A. WILLIUS, J. A. M. A. 99:298, 1932; W. LAWRENCE, I. NEUHAUSER and KATHARINE M. HOWELL, ibid. 99:300, 1932.

An instance of *actinobacillus* bacteremia in a butcher, aged 26, is described. Recovery followed the intravenous injection of sodium cacodylate. *Actinobacillus lignieresii* was isolated from the blood several times.

THE ELECTRICAL CHARGE OF BACTERIOPHAGE. A. P. KRUEGER, R. C. RITTER and S. P. SMITH, *J. Exper. Med.* **50**:739, 1929.

1. Two types of cataphoresis apparatus for determining, under aseptic conditions, the charge carried by biologically active substances, such as bacteriophage, are described. One cell depends on the electrophoresis of particles into agar and their subsequent resuspension in a fluid medium for testing purposes. This cell has certain advantages when employed in connection with agents of small dimensions ordinarily inactivated by prolonged exposure to required test conditions.

2. Several separate races of anti-coli bacteriophage have been found to bear a negative charge within a range of H-ion concentrations from  $p_H$  9.0 to  $p_H$  3.4. At  $p_H$  3.35 and below, the lytic particles migrate through agar to the cathode. It is likely that the reversal in direction of migration is due to the assumption of a positive charge by the bacteriophage corpuscle.

A. P. KRUEGER.

THE PURIFICATION AND CONCENTRATION OF THE VIRUS OF POLIOMYELITIS. A. B. SABIN, *J. Exper. Med.* **56**:307, 1932.

Methods employed by Willstätter and his co-workers in the isolation and purification of enzymes have been applied to the virus of poliomyelitis. Rhoads showed that alumina gel C mixed with poliomyelitis virus in certain proportions at an acid  $p_H$  resulted in the adsorption and inactivation of the virus. The experiments in this communication confirm Rhoads' observation, and show further that the adsorption as well as the inactivation is reversible; i. e., by changing the  $p_H$  to the alkaline side with fifteenth-molar sodium phosphate, it is possible to free the virus in a state in which it is again capable of producing typical poliomyelitis. These experiments show also that by this process the virus undergoes considerable purification by diminution in the concentration of nonvirus-containing substances. Washing the alumina gel C-virus complex with fifth-molar sodium chloride and fifteenth-molar potassium dihydrogen phosphate apparently dissociates no virus, but is capable of freeing a certain amount of extractable organic substances. Furthermore, it is possible to increase the degree of purity and concentration of the virus by distillation in vacuo and subsequent repeated adsorptions and elutions. By such partial purification and concentration, a virus solution with a minimal effective dose (as to the production of typical poliomyelitis) of 0.0003 cc. was obtained. This solution had 0.04 mg. of nitrogen per cubic centimeter, and gave negative biuret, xanthoproteic and ninhydrin reactions. These methods offer an opportunity for the preparation of a quantity of sufficiently purified and concentrated poliomyelitis virus to warrant the beginning of a study of its chemical nature; they also offer a means of anchoring the virus to an insoluble and centrifugatable substance (alumina gel C), which promises to facilitate various immunologic studies, that might otherwise have been impossible.

## AUTHOR'S SUMMARY.

POLIOMYELITIS VIRUS IN SO-CALLED ABORTIVE TYPES OF THE DISEASE. J. R. PAUL and J. D. TRASK, *J. Exper. Med.* **56**:319, 1932.

Experiments are reported which describe the isolation of poliomyelitis virus from the throats of two patients during an attack of so-called abortive poliomyelitis (Wickman type), or what we have termed characteristic minor illnesses in association with poliomyelitis. This finding represents added evidence in favor of the belief, previously held by many observers, that certain types of minor illness which accompany an epidemic of poliomyelitis probably represent mild cases of the disease.

## AUTHORS' SUMMARY.

DEVELOPMENT OF NON-ACID FAST FORMS OF MYCOBACTERIA. F. R. MILLER, *J. Exper. Med.* **56**:411, 1932.

Six strains of mycobacteria—three human strains, Saranac H-37, T. S. and no. 90, a bovine strain, B-1, a smegma strain, no. 74, and a Saranac strain of

*B. phlei*—have been made to grow as nonacid-fast organisms by the addition of a filtered extract of the chromogenic H-37 strain of *B. tuberculosis* to the culture mediums. The action of the extract produced acceleration of growth of the treated culture, followed by macroscopic and microscopic changes, and differentiation into nonacid-fast forms. The bacterial forms grown from these treated cultures were pleomorphic, usually consisting of cocci and small rods, but branching forms and sporelike bodies also developed. The sterility of the extract causing the changes was demonstrated by frequent control inoculations on various mediums, including Kendall's K medium, and autoclaved extracts had the same effects as nonautoclaved. After transfer to mediums suitable for acid growths, four of the strains reverted not only to acid-fastness but to their original cultural characteristics, providing evidence that the nonacid-fast forms were specific for the strain.

#### AUTHOR'S SUMMARY.

DETOXIFICATION OF MENINGOCOCCUS CULTURE FILTRATES. H. M. KLEIN, J. Exper. Med. **56**:587, 1932.

Formaldehyde induces a considerable change in meningococcus culture filtrates. This consists of a marked decrease in toxicity as concerns both the Shwartzman phenomenon and the lethal effect, with relative preservation of the antibody-combining capacity and antigenicity. A similar modification occurs spontaneously in meningococcus culture filtrates on standing. As these changes parallel those occurring in the conversion of diphtheria toxin into toxoid, it is justifiable to consider such altered meningococcus toxin as meningococcus toxoid.

#### AUTHOR'S SUMMARY.

INFECTIOUS MYXOMATOSIS (SANARELLI) IN PREGNANT RABBITS. D. H. SPRUNT, J. Exper. Med. **56**:601, 1932.

Pregnancy in rabbits alters the reactivity of the tissues to the virus of infectious myxomatosis. The livers of pregnant animals with myxomas have a central acidophilic necrosis. Secondary lesions in the lungs are much more numerous and larger in the pregnant than in the nongravid animals. In like manner the lesions in the spleen are more extensive in the pregnant rabbit. On the other hand, the cutaneous lesions of the pregnant animal are decreased in size.

#### AUTHOR'S SUMMARY.

A METHOD FOR THE QUANTITATIVE DETERMINATION OF BACTERIOPHAGE. A. P. KRUEGER, J. Gen. Physiol. **13**:557, 1930.

1. In the case of staphylococcus and antistaphylococcus phage studied, the total volume of the mixture being kept constant, there exists a definite quantitative relationship between C-phage and the time required to reduce a particular concentration of growing phage-susceptible bacteria to an arbitrary turbidity end-point.

2. This relationship furnishes a basis for the quantitative estimation of bacteriophage. A method is described having an accuracy within  $\pm 5$  per cent.

A. P. KRUEGER.

THE KINETICS OF THE BACTERIUM-BACTERIOPHAGE REACTION. A. P. KRUEGER and JOHN H. NORTHROP, J. Gen. Physiol. **14**:223, 1930.

In a study of the reaction between a single strain of *Staphylococcus aureus* and antistaphylococcus bacteriophage occurring in nutrient broth of  $pH$  7.6 at 36 C., the following relationships were shown to hold (the symbols used are: B, bacterium; P, bacteriophage; [B], bacteria/ml; [P], phage/ml;  $B_0$ , initial value of [B];  $B_e$ , [B] at maximal stationary phase of B growth;  $P_0$ , initial value of [P]):

1. Bacterial growth in P-B mixtures does not differ from growth in controls without P except in the case of very high initial P/B ratios, to be noted. There

is no evidence that lytic destruction of B begins shortly after mixing P and B or that B growth is stimulated by P, for the B growth curves in the presence of ordinary P's and controls are identical. Only at the abrupt onset of the lytic process does the B curve of P-B mixture deviate from the control curve.

2. B growth is an essential conditioning factor for P formation.

3. During the logarithmic B growth phase, P formation is also logarithmic, but proceeds at a much faster rate. That is, the percentage rate of increase of P is proportional to the percentage rate of increase of B,  $dP/dt \propto dB/dt \cdot P/B$ . Consequently the statement that each bacterial division produces a certain quantum of P is not correct.

4. There is a definite concentration of phage within the bacterial cell required for production of lysis. This lytic threshold is represented by a concentration of 125 phage units per bacterium.

5. Experimentally the maximal [P]'s of lysates made by mixing a constant initial [B] with widely varying Po's fall within a relatively narrow range. This fact is explained by the large value of  $d \log P/dt$  as compared to  $d \log B/dt$ . That is, the loci of points at which  $\log P = 2.1 + \log B$  (maxima-lysis begins) on the curves of  $\log P$  against  $t$  originating in various [Po]'s will lie at a nearly constant level above the abscissa. Because of this same relationship the maximal [P]'s of such a series will be in the reverse order of magnitude of the Po's; i. e., the larger the Po the smaller will be the maximal [P] attained during the reaction.

6. The lytic destruction of B is logarithmic with time, in this respect being similar to most death rate processes. The value  $-d \log B/dt$  for a particular initial [B] is constant for various initial values of P. There is good evidence that cells need not be growing in order to undergo lysis.

7. During B lysis a considerable percentage of the total maximal P formed is destroyed, the chief loss probably occurring in the intracellular fraction. The major portion (from 70 to 90 per cent) of the final P present after the completion of bacteriophagy is set free during the brief phase of bacterial dissolution.

8. When the entire process of bacteriophagy is completed, the lysates are left with certain [P]'s determined by the completed P-B reaction. The destruction of P during lysis is sufficiently regular to maintain the relationship established at the maximal [P]'s. Therefore the final [P]'s have the same points in common that were noted in 4, as applying to the maximal [P]'s; that is, they all are grouped within a narrow range of [P] values, those having been made with high Po's being of lower titer than those made with low initial [P]'s.

9. There is a significant difference in the temperature coefficients of P and B formation. Further, the temperature coefficients of P and B destruction during lysis differ in almost the same ratio. Consequently, while all experimental evidence postulates B growth as an essential conditioning factor for P formation, the temperature coefficient data suggest that the two processes are basically separate reactions. A similar interpretation holds in the case of B dissolution and P inactivation.

10. The major events in the complete process of "bacteriophagy" are mathematically predictable. The [B] at which lysis occurs under certain standard conditions for given values of Bo and Po may be calculated from the equation:

$$\log B = \frac{2.1 + n \log Bo - \log Po}{n - 1}$$

Substitution of this value for  $\log B$  in the equation

$$t = \frac{1}{gBe} \log \frac{B(Be - Bo)}{Bo(Be - B)}$$

gives satisfactory agreement with observed values for  $t$ -(lysis).

11. The kinetic analysis of the P-B reaction predicts that the values of  $\log Po$  plotted against  $t$ -(lysis) for a constant Bo will give a straight line. This plot is employed in a method for the quantitative estimation of P described in an earlier paper on the basis of experimental observation alone. Its use is made more rational by the facts given.

A. P. KRUEGER.

THE HEAT INACTIVATION OF ANTISTAPHYLOCOCCUS BACTERIOPHAGE. A. P. KRUEGER, *J. Gen. Physiol.* **15**:363, 1932.

The heat inactivation of antistaphylococcus bacteriophage suspended in broth of  $pH$  7.6 at temperatures ranging between 51 and 62 C. proceeds strictly in accordance with the equation for a monomolecular reaction. Consequently, the experimental data furnish no evidence that ordinary phage lysates consist of particles possessing varying degrees of resistance to heat, as Nanavutty found. Nanavutty felt that his experiments strongly suggested the living nature of phage. The present data cannot be so interpreted. For, while it is true that many unicellular organisms follow a logarithmic order of death on exposure to a variety of lethal agents, the inactivation of certain enzymes is similarly an exponential process.

The average value of  $\mu$ , the critical thermal increment, for heat inactivation over the temperature range studied was found to be 101,000. It is therefore of the same order of magnitude as the value of  $\mu$  determined for such processes as the heat denaturation of egg white, the spontaneous destruction of rennet, invertase, vibrio-lysine, etc., and for the cause of death among some bacterial populations.

Very high critical thermal increments for destructive (denaturation) processes apparently occur only in protein compounds. The high value of  $\mu$  for heat inactivation of phage would indicate, then, that protein denaturation is very likely the chief reaction involved in the process. However, it does not necessarily signify that phage is a protein, for it has been shown that the actual lytic material is carried on vehicular particles from which it can be separated under certain conditions. The high value of  $\mu$  may merely mean that the carrier particles possess a high temperature coefficient for heat denaturation and that the change produced in them results in inactivation of attached lytic substance.

A. P. KRUEGER.

STAPHYLOCOCCUS AUREUS: DISSOCIATION AND ITS RELATION TO INFECTION AND TO IMMUNITY. R. E. HOFFSTADT and G. P. YOUNMANS, *J. Infect. Dis.* **51**:216, 1932.

From this study it may be concluded: that *Staphylococcus aureus* can be dissociated into S, R and G forms; cross-agglutination and cross-complement fixation are found for all these forms; that treatment with heat-killed cultures of the "whole" or of the dissociated forms does not affect the power of invasion of either the "whole" or the dissociated forms; that three forms were dissociated with physiologic variation; that the dissociated forms apparently are only part of a normal cycle of changes through which the organism passes, and that the persistence of the avirulent form in the body of the animal may explain how the organism lurks in the body without manifestations and later, when virulence returns, appears again with lesions.

AUTHORS' SUMMARY.

PNEUMONIA IN CHILDREN. M. L. MENTON, S. F. BAILEY and F. M. DEBONE, *J. Infect. Dis.* **51**:254, 1932.

Bacteriologic studies on lungs from one hundred and thirty-one autopsies showed a high incidence of mixed cultures, with considerable individual variation. *Streptococcus viridans* was found in 50 per cent and *S. haemolyticus* in 23.7 per cent of the lungs. Both types occurred in 6.9 per cent of the cases. The pneumococcus invariably occurred in association with other bacteria, and was isolated in 45.8 per cent of the cases. The incidence of type 4 (heterogenous group) among these was 81.6 per cent. There was a decreasing frequency of this type with advancing age, namely, 82.6 per cent for less than 2 years, 71.6 per cent for between 2 and 6 years and 50 per cent for between 6 and 14 years. The gross and microscopic appearance of the greater number of the lungs was typically that of bronchopneumonia. Acute, rapidly developing pulmonary infection frequently gave characteristic gross signs. Infection with the streptococcus was characterized by small subpleural focal hemorrhages; infection with *Bacillus influenzae* by intense con-

gestion, hemorrhage and fibrinous pleurisy, and infection with pneumococcus by sharply circumscribed areas of consolidation, the surface of which was depressed below that of the surrounding tissue. In the more chronic infections, or when many associated organisms were present, these signs were either masked or entirely lacking.

AUTHORS' SUMMARY.

INDUCTION OF AVIRULENCE IN PASTEURELLA TULARENSIS. L. FOSHAY, J. Infect. Dis. **51**:280, 1932.

Evidence is presented to show that two strains of *Pasteurella tularensis*, from two fatal cases in man, lost their virulence for certain laboratory animals as a result of prolonged cultivation on coagulated egg yolk at low temperature.

AUTHOR'S SUMMARY.

BLOOD CULTURES OF APPARENTLY HEALTHY PERSONS. A. F. REITH and T. L. SQUIER, J. Infect. Dis. **51**:336, 1932.

Samples of blood from 293 apparently healthy persons were cultured. Cultures containing streptococci, diplococci, diphtheroids, *Micrococcus catarrhalis*, colon bacilli and obligatory anaerobic rods were considered positive. Positive cultures were obtained from 53, or 27 per cent, of 194 persons who had chronic focal infection, while positive cultures were obtained from only 12 per cent of 99 persons who had no demonstrable focus of infection. Pain in the joints or muscles, including chronic infectious arthritis diagnosed clinically in 7, was present in 24. Ten, or 42 per cent, of these gave blood cultures positive for streptococci or diplococci. A seasonal variation in the incidence of positive blood cultures from persons without demonstrable foci of infection suggests that acute respiratory infections may be responsible for some of the positive cultures.

AUTHORS' SUMMARY.

### Immunology

DIAGNOSIS OF TULAREMIA BY MEANS OF THE INTRADERMAL REACTION. L. FOSHAY, J. Infect. Dis. **51**:286, 1932.

The intradermal test is the earliest available diagnostic aid for determining the presence of tularemia. Positive reactions have occurred as early as the fourth day of illness, i. e., practically a week before agglutinins usually appear in the blood. The test is useful at any time during the first year following infection. The allergic skin response is specific and reliable. Positive reactions are constant in the presence of tularemia, but do not occur in normal persons or in the presence of certain other acute infections. The positive reaction becomes negative as a result of artificial desensitization. This change appears to coincide with and to depend on the induction of adequate immunity. The method used to desensitize has not produced a subsequent state of resensitization during the next succeeding seven months. Further proof is presented that chemical detoxication of bacterial bodies can be carried to a reasonably satisfactory degree without noticeably impairing their antigenic properties. Natural desensitization in tularemia has not been noted during the first year following infection. Daily subcutaneous injections of detoxified vaccine seem to have shortened the course of the disease in three cases; however, this does not seem at present to be an ideal form of treatment.

AUTHOR'S SUMMARY.

IMMUNOLOGIC STUDIES ON TULAREMIA IN RABBITS. C. M. DOWNS, J. Infect. Dis. **51**:315, 1932.

Formaldehydized cultures of *P. tularensis* produce a high degree of immunity in rabbits. This immunity is evidenced by: delay of invasion of the blood stream by the organisms, the production of agglutinins in the blood stream and the marked proliferative and localizing changes shown in the lesions in immune animals as

contrasted with normal controls. This immunity develops slowly after from six to eight injections. Subcutaneous, intracutaneous or intravenous methods seem equally effective. A similar method of immunization might be effective in man.

AUTHOR'S SUMMARY.

NEUTRALIZING EFFECT OF POOLED HUMAN SERUM ON THE POLIOMYELITIS VIRUS. N. P. HUDSON and E. H. LENNETTE, *J. Prev. Med.* **6**:335, 1932.

Ten specimens of pooled serum from city-dwelling adults and from persons of various ages convalescent from poliomyelitis were tested for their neutralizing effect on the poliomyelitis virus. The numbers of persons contributing to the pools varied from five to fifty. All specimens manifested neutralizing properties when the serum was undiluted and frequently when examined in dilutions of 1:5 and 1:25. This type of biologic technic does not allow for exactitude in interpreting comparative titers when the differences are so small, as was demonstrated by the two types of serum in these experiments. The research laboratory can function to advantage in cooperation with clinical investigations into the efficacy of therapy in poliomyelitis with serum from convalescents and so-called normal adults. Further inquiry is necessary to determine whether there is any relation between the possible benefits in serum therapy and the experimental capacity of serum to neutralize the effect of the virus. AUTHORS' SUMMARY.

A TOXIC SUBSTANCE IN THE FECES AND URINE IN POLIOMYELITIS. J. A. TOOHEY, *J. Prev. Med.* **6**:379, 387 and 397, 1932.

Evidence is presented of the presence in the feces and urine of patients with poliomyelitis of a substance that is toxic for guinea-pigs. The most marked reactions in the guinea-pigs were found in the small intestines, suprarenals and spinal cord. In the cord the changes resembled the changes in the cord in man after an attack of poliomyelitis. Convalescent poliomyelitis serum protected guinea-pigs against the toxic action of the substance.

ANTIHAEMOLYSINE TITRES IN HAEMOLYTIC STREPTOCOCAL INFECTIONS AND THEIR SIGNIFICANCE IN RHEUMATIC FEVER. E. W. TODD, *Brit. J. Exper. Path.* **13**:248, 1932.

A consistent increase of antistreptolysine occurs in the blood after infection by hemolytic streptococci. This increased titer is found in simple, uncomplicated infections and in infections followed by rheumatic fever. Equally high antistreptolysine titers occur in patients with rheumatic fever who have been shown by cultures to be infected by hemolytic streptococci, and in patients with rheumatic fever who have not been examined bacteriologically. This supplies immunologic evidence that rheumatic fever is preceded by hemolytic streptococcal infection.

AUTHOR'S SUMMARY.

BACTERICIDAL POWER OF NORMAL SERUM. J. GORDON and H. S. CARTER, *J. Path. & Bact.* **35**:549, 1932.

Adsorption of normal guinea-pig and rabbit serums with heated and washed bacterial suspensions at 0 C. removes from the serums the bactericidal power against a number of organisms. This adsorption is in no sense specific, because the bactericidal power of the serum for the least sensitive organisms is removed first, and that for the more sensitive organisms is removed later. It is suggested that the bactericidal power of normal serum against various organisms is not due to the presence of specific natural antibodies. Our results support the opinion of Muir that variations in the bactericidal power of normal serum against different organisms depend on the sensitiveness of these organisms to nonspecific factors in serum (complement plus a heat stable factor). AUTHORS' SUMMARY.

THE PRECIPITATION OF DIPHTHERIA TOXOID BY METALLIC SALTS. M. L. SMITH, *J. Path. & Bact.* 35:663, 1932.

Diphtheria toxoid can be precipitated from solution by salts of most metals having insoluble hydroxides, by some phosphates and by various gelatinous precipitates. The toxoid can in most cases be recovered by elution in phosphate solution or solution in sodium tartrate or citrate. Toxoid precipitated by various precipitants and at various hydron concentrations is from five to fifty times as pure as the original. The yields of specific toxoid are in most cases from 70 to 95 per cent. Evidence is produced that the toxoid is adsorbed onto the gelatinous precipitate of the hydroxide, the phosphates and the various gelatinous precipitates. The washed precipitates are in general better antigens than the original toxoid, the best results being obtained from precipitates of colloidal aluminium hydroxide, zirconyl chloride, calcium phosphate and alum. Combination of acid precipitation and precipitation by metallic salts results in an efficient antigen with a high degree of purity.

## AUTHOR'S SUMMARY.

THE PRODUCTION OF SPECIFIC BACTERIOTROPINS IN INFECTIONS WITH HAEMOLYTIC STREPTOCOCCI. R. HARE, *J. Path. & Bact.* 35:701, 1932.

Bacteriotropins for the homologous organisms have been shown to be present in the serum of cases of hemolytic streptococcal infection of the uterus before the fall of temperature. The length of time they persist during convalescence is probably dependent on the severity of the infective process. They are not present in the serum of rapidly fatal cases but do appear during the later stages of more chronic but fatal infections. Death is not preceded by a fall in bacteriotropic immunity.

## AUTHOR'S SUMMARY.

## THE HAEMOLYTIC STREPTOCOCCI: THEIR GROUPING BY AGGLUTINATION.

F. W. ANDREWES and E. M. CHRISTIE, Medical Research Council, Special Report Series, no. 169, p. 71. London: His Majesty's Stationery Office, 1932.

The main object of the research has been to ascertain, by using the more refined methods of antigenic analysis, whether it was possible to construct a grouping of hemolytic streptococci likely to be of practical value in clinical work, and especially to see whether serologic varieties could be correlated with apparently distinct diseases. It was soon clear that agglutination tests by themselves would prove a weak reed. For accurate antigenic analysis, quantitative agglutinin-absorption tests were imperative. Much work was necessary to devise the best method of preparing suitable emulsions of streptococci for agglutination tests. The attack on this difficulty led to a study of the acid-agglutination of streptococci, and astonishing facts were brought to light concerning the effect of the final—and even of the penultimate—culture medium on the acid-agglutinability and serologic behavior of the organisms. In work of this sort many serious pitfalls can be avoided only by a recognition of the extreme variability of *Streptococcus pyogenes*. It appears that more or less rough and smooth colonies may be picked from a plate, but that these must not be supposed to correspond with the rough and smooth forms of *B. coli* and *Salmonella*. Commonly the rough variants are the more virulent, but the reverse may be true. Commonly, also, the rough form is the more specific, and the smooth the group form, but there are exceptions to this rule, too. Single strains of cocci such as the Dochez strain may change greatly on cultivation, and serums prepared against one strain at different times may be found to have different properties. Organisms and serums with pronounced "group" properties may lead the unwary astray. Some of the technics advised for preparing good agglutinable emulsions actually tend to the production of "group" forms. Thus it may happen that a worker who has, as he imagines, recognized a serologic type of streptococcus associated with a certain disease, has actually been deceived through working with a serum which is largely "group" in character. Something about these group and specific races was learned by means of absorptions with single adequate doses, but far more was revealed by absorptions with graduated

doses of organisms and by mirror absorptions. From these it appeared that only exceptionally are two strains of streptococci serologically identical, and rarely are they entirely dissimilar. Almost always there is more or less group antigen in common between them; there are even definite hints that more than one group antigen exists. There is a wide basis from which such conclusions can be drawn, for about 125 graduated absorptions and about 630 ungraded absorptions have been carried out. This general study of the racial interrelationships of hemolytic streptococci led to a more detailed antigen analysis of certain strains, particularly Griffith's four major scarlet fever types. The individuality of his types I, II and IV was readily confirmed. It was otherwise with his type III, which did not seem entitled to rank beside the others as a distinct entity, but was rather predominantly of group form. The Dochez strain appeared also to be a distinct variety, though it seems to be uncommon in this country. Other strains from scarlet fever were "serological singletons." Apparently no one serologic form of streptococcus can be credited with the causation of scarlet fever, though three or four recognizable serologic types seem to be found in it with extraordinary frequency. No distinct types stood out from a miscellaneous assortment of puerperal, surgical and erysipelas strains of streptococci, though an occasional representative of Griffith's scarlet fever types I and II was found among them. The literature concerning the serologic classification of hemolytic streptococci is most confusing. Each worker has used a different technic and has made no attempt to correlate his results with those of his forerunners. Others may yet attempt the Herculean task. It is hoped that the work here recorded may be of some service to them, and that some of the many pitfalls have been revealed. A serologic study by methods more accurate and quantitative than most workers have used has failed to bring order out of chaos. "The more one studies haemolytic streptococci the more strongly is the impression gained that they are in a state of constant flux in which it is difficult to find any firm foundation for a permanent systematic classification."

#### AUTHORS' SUMMARY.

A METHOD FOR SEPARATING ANTIBODIES FROM SERUM PROTEINS (PROTEIN-FREE ANTIBODY). MAX FRANKEL, Proc. Roy. Soc., London, s. B, **111**:165, 1932.

Directions are given for the separation of flagellar agglutinin from dilutions of antityphoid serum through adsorption on kaolin and subsequent extraction of the adsorbate with a solution of salt and an amino-acid. Kaolin is a clay the active principle of which is hydrated aluminum silicate. The extracts are reported to retain from 12 to 24 per cent of the agglutinin originally present in the serum and to lose none of their potency on dialysis, evaporation to dryness, under diminished pressure or on extraction of the dry residue with ether. No figures for the comparative amounts of solid or nitrogenous substance carried into the final preparations, per unit of immune activity, are given. The preparations gave no demonstrable chemical test for protein, were not impaired by incubation with pancreaticin and did not sensitize guinea-pigs to anaphylactic shock. Detailed descriptions of the tests are not given, nor are control tests described for solutions of protein similarly treated and equivalent in total solid content to the immune preparations examined. No mention is made of the pertinent work of Ottenberg and Stenbuck, Huntoon, and Locke, Main and Hirsch. The first-named investigators concentrated the immune substances of typhoid agglutinating serum by the method of adsorption on homologous antigen, following each step of the fractionation with nitrogen values. Their final preparations contained but from  $\frac{1}{125}$  to  $\frac{1}{250}$  as much nitrogen as the original serums. Huntoon, using a similar method, accomplished an 860-fold concentration of the protective antibodies in anti-pneumococcus serum. His preparations, like Frankel's, resisted the action of trypsin, but did sensitize guinea-pigs to anaphylactic shock when injected in sufficient quantity. Locke, Main and Hirsch accomplished a 1500-fold concentration of the immune substances of a rabbit anti-sheep hemolytic serum. Their preparations sensitized guinea-pigs to anaphylactic shock when injected in amounts

equivalent to those in which a dilution of whole serum, of comparable nitrogen content, elicited sensitization. The first investigator to use an aluminum-containing adsorbent for the fractionation of an immune serum was Hans Aronson, who in 1893 obtained preparations of diphtheria antitoxin in a dry, but still active, state which contained from  $\frac{1}{75}$  to  $\frac{1}{100}$  as much total solids, per unit of immune activity as the serum from which they were derived.

ARTHUR LOCKE.

**POSITIVE SEROREACTIONS FOR SYPHILIS FOLLOWING INJECTION OF ANTI-DIPHTHERIA SERUM.** C. STERN, München. med. Wchnschr. **79**:583, 1932.

Positive reactions for syphilis occur after infections in the throat, in infections caused by oral spirochetes and by spirochetes of balanitis, in diphtheria-like conditions and especially after antidiphtheritic serum treatment. Generally, such positive reactions disappear rapidly; occasionally, they persist longer, if infectious foci in the tonsils remain. The importance of using proper judgment in evaluating the results of serosyphilitic reactions is thereby emphasized.

B. S. LEVINE.

**SITE OF FORMATION OF ANTIBODIES IN RABIES.** E. LÖFFLER and F. SCHWEINBURG, Virchows Arch. f. path. Anat. **283**:540, 1932.

In a previous report the authors presented the conclusion that the tissues of the central nervous system take no part in the development of immunity against rabies. To determine the part that the reticulo-endothelial system may take in the development of the immune state, the method of blockade was used. The animals in whom the blockade had been made remained unprotected. The serum of such animals had only slight virucidal action. The authors conclude that protective immunity against rabies is the result of the activity of the reticulo-endothelial system.

O. T. SCHULTZ.

### Tumors

**DOES LACK OF MAGNESIUM AFFECT TRANSPLANTABLE TUMORS IN RATS?** R. E. GARDNER, E. R. ORENT, E. V. MCCOLLUM and R. R. HYDE, Am. J. Hyg. **16**: 323, 1932.

When sixty rats, the hosts of transplanted carcinoma or sarcoma, were placed on diets with very small magnesium content, signs of magnesium deficiency resulted, but no inhibition of tumor growth.

RALPH FULLER.

**HISTOLOGY OF MELANOMA.** N. C. FOOT, Am. J. Path. **8**:309 and 321, 1932.

An examination of a series of pigmented nevi by means of silver impregnations of several types uniformly confirmed Masson's theories that nevus cells are derived from those of the sheath of Schwann, nonpigmented in their pristine state, associated with nerve trunks and fibers, and closely related to those of the neurofibroma.

By means of Rogers' technic of silver impregnation, nerve fibers have been demonstrated in melanomas and a striking resemblance shown between Masson's *lames foliacées* and the normal Meissner corpuscles, not only in morphology (which Masson has already brilliantly shown), but also in distribution of nerve filaments in and about them. This article reenforces what was said in the preceding one and supplies some of the deficiencies noted in that paper, due to lack of a suitable method for attacking the problem.

AUTHOR'S SUMMARIES.

**A CASE OF MULTIPLE PAPILLOMATA OF THE LARYNX WITH AERIAL METASTASES TO THE LUNGS.** H. B. HITZ and E. OESTERLIN, Am. J. Path. **8**:333, 1932.

In a girl, aged 2, multiple papillomas of the vocal cords became detached and were carried into the bronchi by aspiration. They passed the larger bronchi, but

were caught in the bronchioli, obstructing the lumens. In this way, they became implantation metastases and began to grow in the alveoli. No invasion of the lymphatics by tumor cells was observed.

EXPERIMENTAL AND SPONTANEOUS SCHWANNOMA (PERIPHERAL GLIOMA).  
P. MASSON, Am. J. Path. 8:367 and 389, 1932.

*Experimental Schwannoma.*—In the first experiment (Nageotte), the sciatic nerve of a rabbit is cut and the upper end torn out to prevent regeneration of neurits from above. A second incision is made 1 cm. below the first and the fragment left in place. A tumor forms at each end of the fragment. In the second experiment, a piece 1 cm. long is removed from the sciatic nerve of a rabbit and transplanted alongside of the intact sciatic nerve of the other side. From each end of the transplant there grows a tumor which may reach an enormous size and invade the surrounding tissue like a malignant growth.

If sections of these tumors are studied with a differential stain, such as the Masson-Mallory trichrome, which distinguishes cytoplasm from collagen, it is at once obvious that one is dealing with something more than simple fibrous connective tissue. There is a network of cytoplasmic cylinders sheathed with collagen. Masson shows that the cylinders are outgrowths from the schwannian syncytia of the cut ends of the nerves. Using Laidlaw's silver technic for endoneurium, he demonstrates an argyrophil web around the cylinders exactly like the Plenk-Laidlaw sheath of normal endoneurium. The transformation of the schwannian syncytium into a network takes place both inside of the nerve fragment and in the tumors. The successive steps are, first, amitotic division of the schwannian nuclei, next longitudinal cleavage of the cylinders, and finally the formation of collagen sheaths around each daughter cylinder. The production of this collagenous endoneurium is directed exclusively by the schwannian syncytium without the intervention of fibroblasts.

*Spontaneous Schwannoma.*—Here the same trichrome and silver technics are applied to the encapsulated tumors of the peripheral nerves, known in this country as peripheral fibroblastoma but called by most continental pathologists neurinoma, schwannoma or peripheral glioma. Masson shows that these tumors consist of a network of branching cytoplasmic cylinders sheathed with a collagenous endoneurium exactly like the amputation schwannomas. These tumors grow in exactly the same way by division of the schwannian nuclei, cleavage of the cytoplasmic cylinders and the formation of a collagenous sheath around each daughter cylinder.

The well known palisading results from longitudinal division of the nuclei preparatory to multiple cleavage of the schwannian cylinder. Masson describes certain tumors in which the schwannian nuclei arrange themselves at the periphery of the cylinder. Here cleavage is crosswise, resulting in the formation of structures resembling Wagner-Meissner tactile corpuscles, as he has already described in pigmented moles. He suggests that the schwannian syncytium of these fibers has undergone a differentiation which presumably belongs exclusively to sensory nerve fibers.

The encapsulated tumors of the peripheral nerves are not fibroblastomas. They are schwannomas; or, accepting the views of Held, Nageotte and other neurologists that the schwannian cell system is a peripheral neuroglia, they are peripheral gliomas. These tumors contain collagen on the same terms as central gliomas, no more and no less. The only collagen of mesodermal origin in these tumors is the collagen of the walls of the vessels. Just as in amputation schwannomas, their collagenous endoneurial sheaths are laid down under the direction of the Schwann cells. Fibroblasts appear later and populate the collagenous framework which has been prepared for them. The paper is a clear statement of his views by a leading pathologist of France.

GEORGE F. LAIDLAW.

ADAMANTINOMA OF THE JAW WITH ASPIRATION METASTASES TO THE RIGHT LUNG. J. VORZIMER and D. PERLA, Am. J. Path. 8:445, 1932.

The bronchi of the lower lobe of the involved lung were markedly dilated and their lumens filled with casts of the tumor tissue. In places the parenchyma of the

lung was invaded. It is suggested that the tumor tissue was aspirated into the lung from the primary tumor, via the trachea and bronchial tree, and grew primarily within the lumens of the bronchi. No similar metastasis of an adaman-tinoma in the lung was found reported in the literature.

## FROM AUTHORS' SUMMARY.

DIAGNOSIS OF INTRACRANIAL TUMORS BY SUPRAVITAL TECHNIC. LOUISE EISEN-HARDT, *Arch. Neurol. & Psychiat.* **28**:299, 1932.

A supravital technic described by Eisenhardt and Cushing (*Am. J. Path.* **6**: 541, 1930), has proved of great value especially in emergency cases. In one instance, a correct diagnosis of a tumor was made from the scanty amount removed by lumbar puncture. Good photographs are presented of cells of ten cerebral tumors—meningioma, medulloblastoma, neurinoma, astroblastoma and glioblastoma—and contrasted with those of the same types of cells obtained from fixed specimens. In many cases, the contrast is striking, as in the supravital staining the influence of hardening procedures is removed.

GEORGE B. HASSIN.

THE REDUCING POWER OF CERTAIN TUMORS. E. S. G. BARRON, *J. Exper. Med.* **55**:829, 1932.

The tissues of Rous chicken sarcoma and of the infectious myxoma of the rabbit do not possess the oxidation-reduction enzyme succinodehydrogenase, which is present in normal tissues and in transplantable tumor. Filtrable virus diseases (rabbit virus III, rabbit neurovaccine, rabbit herpes, fowl-pox) produce in the tissues affected by them a partial inhibition of succinodehydrogenase.

## AUTHOR'S SUMMARY.

PROPERTIES OF THE CAUSATIVE AGENT OF A CHICKEN TUMOR. J. B. MURPHY and others, *J. Exper. Med.* **56**:91, 107 and 117, 1932.

By two methods a protein fraction can be separated out from a chicken tumor I extract, which carries all the tumor-producing agent. The precipitate can be dissolved and reprecipitated a number of times without loss of activity. Aluminum hydroxide will adsorb the protein from the extract and leave the agent behind. This purified material has a very low protein content, if any, as shown by both chemical and biologic tests.

An inhibiting substance in the tumor is shown by the fact that the product of desiccation of the tumor is more active after it has been washed two or three times with water, and by the fact that an extract of the tumor is more potent after some factor is removed by adsorption on aluminum hydroxide. When the tumor-producing factor in an extract of a slow-growing tumor has been destroyed by heating at 55 C., it is found to have the property of neutralizing a highly active tumor extract. This inhibiting property is destroyed by heating over 65 C.

The injection of these extracts and their active protein fractions into rabbits induced the formation of precipitins and neutralizing antibodies. When the major portion of the proteins in the extracts had been eliminated, the latter induced the formation of neutralizing antibodies, but not of precipitins. The tumor agent, more highly purified by removal of the viscous fraction, did not induce precipitins, and only two of the fifteen serums gave evidence of neutralizing bodies. After the removal of the major portion of protein, the extracts showed insufficient interaction with the serums to fix complement.

## AUTHORS' SUMMARIES.

COMBINING AFFINITIES IN BACTERIAL VARIATION AND CARCINOGENESIS. A. EASTWOOD, *J. Hyg.* **32**:301, 1932.

Some of the principles which are gradually coming to light in bacterial variation may ultimately be of assistance in the much more obscure problem of the change from the normal mammalian cell to its malignant variant. I refer in particular

to conceptions about the mechanism of cellular growth and the nature of a cell's combining affinities. Mammalian cells possess considerable capacity for self-regulation and, in this respect, may be compared with bacteria as regards both their synthetic activities and their surface "mosaic" of combining "centres," some of which are capable of readjustment and thus constitute a predisposing cause of variation. Systemic control, so far as it stimulates or restrains growth, may be explained as a readjustment of combining affinities on the surface of the cell. Another important aspect of systemic control over animal cells is the requirement that these must retain the characters peculiar to their species. This influence of the plasma may be compared to natural immunity toward bacteria; the plasma is not equipped with specific antibodies, but its activities seem to be incompatible with the synthetic activities of the heterologous cell, the result being that the cell's protein cannot execute its rhythmic cycle of growth. The cancer variant does not appear "spontaneously"; some extrinsic influence,  $x$ , is necessary. But "spontaneity" may be conceded to this extent that there may be spontaneous change of certain cells into a state of susceptibility toward  $x$ , which may initiate the precancerous condition. Taking a broad view of the various circumstances which may induce the precancerous state, it does not seem possible to regard  $x$  as a special substance which acts directly on the cells in question. More probably  $x$  is a changed condition of local environment consequent on chronic irritation. On this view, a known carcinogenic chemical compound does not act directly on the cells but indirectly, by bringing about a change in environment. Carcinogenesis may be divided into two stages: (a) There is a degenerative change, involving loss of some surface combining affinities; this, according to my hypothesis, is not merely a loss but involves a rearrangement of surface groupings, with consequent appearance of new and abnormal combining centers. These changes constitute the precancerous condition. (b) There is a further change which invests these cells with the invasive equipment of malignancy. The latent period is occupied with *a*. About what actually happens one can only offer surmises. My suggestion is that localized chronic irritation leads to a change in the adjacent endothelium, with the result that the plasma filtered into this area is abnormal and gradually produces the precancerous change in certain susceptible cells. These cells lose the combining affinities which, on termination of the latent period, would make them susceptible to systemic control of growth, and acquire different and abnormal combining centers. The influences which may produce these changes in the plasma cannot be attributed to any one substance, but must be regarded as nonspecific. But it is not necessary to assume that the whole of the carcinogenic process is nonspecific. A specific factor may be operative in *b*, the change from the precancerous to the definitely malignant cell. My suggestion, which I have discussed in the light of certain bacteriologic analogies, is that some of the abnormal combining centers of the precancerous cell are antigenic and, on the termination of the latent period, produce an antibody which is specific for surviving precancerous cells and changes them into the malignant condition.

#### AUTHOR'S SUMMARY.

**SOLITARY PLASMOCYTOMA.** M. J. STEWART and A. L. TAYLOR, *J. Path. & Bact.* **35:541, 1932.**

Four cases of solitary plasma cell tumor (plasmocytoma) are described which occurred in the upper third of the humerus, in the maxilla, in the soft palate and in the floor of the mouth. That in the humerus was associated with pathologic fracture and was treated by amputation; the others were treated by local excision. In all cases a complete cure was effected. In cases 1 and 2 the patients were alive and free from recurrence eight years after operation; in case 3 the patient died of an independent malady after several years, and in case 4 the patient was alive and well after three years. These cases make an appreciable addition to the scanty evidence at present available that there occurs a solitary form of plasma cell tumor, both in bone and in the upper air passages, which in a majority of cases shows at most but local malignancy and is amenable to local operative treatment, perhaps also to radiation therapy. Solitary plasmocytoma of bone is likely to be

mistaken clinically for endosteal tumor of high grade malignancy, and the desirability of a biopsy before resorting to radical surgical treatment is stressed.

AUTHORS' SUMMARY.

**PRIMARY CARCINOMA OF THE LIVER.** J. C. TULL, *J. Path. & Bact.* **35:557**, 1932.

Primary carcinoma of the liver is comparatively frequent among natives of certain provinces in Southern China. It is a disease of middle age and usually reaches an advanced stage before symptoms appear. Flukes are not commonly present. Cirrhosis of the liver is present in the great majority of cases, especially in those of hepatic cell type. The latter type is nearly three times as common as the biliary duct type. The right lobe of the liver is much more frequently involved than the left, but the gallbladder is seldom affected. The liver may be riddled with new growth and still function normally, as judged by various functional tests. Metastases are less frequent than with primary carcinomas of other organs. Splenomegaly is often present.

AUTHOR'S SUMMARY.

**CHORIONEPITHELIOMA OF THE TESTIS.** J. M. ROSS, *J. Path. & Bact.* **35:563**, 1932.

A case of testicular tumor is described in which the pulmonary metastases consisted of tissue morphologically identical with typical chorionepithelioma. The primary tumor, though of small size, was largely necrotic. In the abdominal metastases, the origin of syncytium and Langhans' cells could be traced to small, cuboid, darkly staining cells, which also gave rise to carcinomatous tissue, and were found in blood vessels, lymphatics and the peripheral sinuses of lymph glands. In the cervical glands, these cells gave rise to columnar epithelium and other structures. The conclusion is reached that the formation of "chorionepithelioma" testis is the expression of a process of specific partial differentiation of these pluripotential cells.

AUTHOR'S SUMMARY.

**INTRANUCLEAR "INCLUSION BODIES" IN GLIOMAS.** D. S. RUSSELL, *J. Path. & Bact.* **35:625**, 1932.

Intranuclear inclusion bodies have been found in 33 per cent of a series of 192 gliomas. They were chiefly present in examples of spongioblastoma multiforme, 61 per cent of which showed this change. Similar bodies have been found in the liver in a relatively large proportion of cases of Hodgkin's lymphogranuloma and in a small proportion of deaths from various causes. They appeared to be formed most probably by alteration of nucleoli, but origin in the nucleoplasm could not be excluded. No association was found with atypical development of cells or with ordinary degenerations of cells and their nuclei. The bodies resemble the intranuclear inclusions characteristic of certain virus infections. The observations recorded are compatible with their being expressions of virus infection. If they are such, their frequency in the gliomas points to a virus being the cause of these growths.

AUTHOR'S SUMMARY.

**MULTIPLE TUMORS OF THE STOMACH.** M. PLONSIKER, *Centralbl. f. allg. Path. u. path. Anat.* **54:49**, 1932.

Fibro-adenomatous tumors were found in six sites in a stomach altered by chronic gastritis. All the tumors were gray-red, broad-based, fixed, papillary and projected above the mucosa from 1 to 2 cm. One tumor, 3 by 2 cm., was on the lesser curvature 1.5 cm. distal to the cardia; one was at the middle of the lesser curvature, 3 cm. in diameter, and 2 cm. removed from this toward the pylorus was the largest tumor, 5.5 cm. in diameter. Others occurred in the prepyloric region and in the middle of the front wall. A cross-section of the gastric wall remote from the tumors showed the muscularis from 0.2 to 0.3 cm., the submucosa from 1 to 1.5 cm., and the mucosa 0.5 cm. thick.

GEORGE RUKSTINAT.

A NEURO-EPITHELIOMA OF THE LUNG. W. ANDRUS, Centralbl. f. allg. Path. u. path. Anat. **54**:195, 1932.

Andrus reports the microscopic characteristics of a benign tumor, 4.5 cm. by 2.5, which was removed from the right lung of a 23 year old woman. She had had pulmonary symptoms several times in the three years preceding operation and these had been attributed to bronchitis, pleurisy, pneumonia and tuberculosis. The tumor was situated close to a bronchus, was well encapsulated and was composed of spongioblastic elements, in which rosettes and ganglion cells with well developed cell processes were evident.

GEORGE RUKSTINAT.

### Medicolegal Pathology

ACCIDENTAL, FATAL LACTIC ACID POISONING. H. FÜHNER, Samml. v. Vergiftungsfällen **3**:71, 1932.

A 27 year old woman, in whom drainage of the gallbladder via a duodenal tube had been instituted for diagnostic purposes, was given 100 cc. of 33 per cent lactic acid through the tube instead of magnesium sulphate solution. Pain started in the right upper quadrant immediately, and was followed by vomiting, which did not alarm the nurse, since the patient had retched and vomited at intervals after the insertion of the tube. Death occurred in twelve hours, and at autopsy hemorrhages were found in a confluent region in 23 cm. of the small bowel and in a goose egg-sized collection beneath the serosa of the back wall of the stomach. In the duodenum the furrows between the folds of mucosa were necrotic and filled with a crumbly material. Microscopically, there was thrombosis of many of the vessels in the small bowel, and leukocytic infiltrations were present in all coats of the wall. A total of 3.82 Gm. of lactic acid was recovered from portions of various organs, and an estimate based on the weight of the organs indicated recovery of 17 Gm. of the acid. The author indicates that some of this lactic acid was probably a physiologic accumulation.

GEORGE RUKSTINAT.

FATAL MEDICINAL POISONING WITH CHENOPODIUM OIL. G. SCHRADER, Samml. v. Vergiftungsfällen **3**:79, 1932.

A 4½ year old child was given a capsule containing 16 drops of chenopodium oil as a vermifuge, and two days later was given 32 drops, since the first dose had been ineffective. Death occurred in about twenty-two hours, after a period of illness characterized by convulsions, cyanosis and coma. At necropsy, the small bowel was markedly inflamed; the solitary lymph nodes and Peyer's patches were hyperemic, as were also the mesenteric lymph nodes, the brain and the meninges. Status thymicolymphaticus was a contributory factor. Chenopodium oil was recovered from various organs. In this instance the maximum adult dose of 0.5 Gm. had been exceeded in a child.

GEORGE RUKSTINAT.

FATAL ARBOR VITAE POISONING THROUGH EMPLOYMENT OF THE TWIGS AS AN ABORTIFACIENT. G. JUNGMICHEL, Samml. v. Vergiftungsfällen **3**:89, 1932.

A servant girl, who was suspected of being pregnant by her mistress, was found unconscious on the floor, in convulsions and frothing at the mouth. A bulb injector and tubing lay between her legs and nearby was a basinful of a green infusion, which was inadvertently thrown out. The infusion was later proved to be an infusion of arbor vitae twigs, which the servant had drunk as tea for about a month and had then employed as a douche. Rapid absorption from the vagina apparently added the necessary lethal dose, which caused death in two days. At necropsy an intact 3 months' fetus existed, and in addition the following pathologic changes were found: bilateral pneumonia, hemorrhage into the myocardium, cloudy swelling of the parenchymatous organs and fatty degen-

eration of the liver and kidneys. Of the four instances of poisoning with this plant recorded in the last ten years, fatalities resulted in two.

GEORGE RUKSTINAT.

**SUICIDAL COPPER SULPHATE POISONING.** J. BALÁZS, Samml. v. Vergiftungsfällen **3:99**, 1932.

Death occurred in ten hours in a woman who dissolved about 20 Gm. of copper sulphate in water and drank the solution. The blood vessels, post mortem, were filled with dry coagula. The following figures give the copper sulphate contents in grams per hundred grams of material:

Stomach content .....	0.2
Bowel content .....	0.05
Liver .....	0.02
Spleen .....	0.012
Kidney .....	0.008
Blood .....	A trace

GEORGE RUKSTINAT.

**SUICIDAL POISONING WITH AMMONIA.** J. BALÁZS, Samml. v. Vergiftungsfällen **3:101**, 1932.

A woman, aged 20, took twenty-three powders containing mostly acetylsalicylic acid; she vomited these in a short time. Then she drank about 100 cc. of commercial spirits of sal ammoniac; she became unconscious and died four days later. Death was due to bronchopneumonia, but the epiglottis, stomach and bronchi were partially corroded. The epiglottis was so badly damaged that the cartilage was involved.

GEORGE RUKSTINAT.

**FATAL MEDICINAL POISONING BY NUPERCAINE-CIBA.** F. TIMM, Samml. v. Vergiftungsfällen **3:215**, 1932.

A man died from thirty to forty minutes after receiving an intra-urethral injection of 10 cc. of a solution of nupercaine, in preparation for cystoscopy. Subsequently, it was found that the total quantity of nupercaine injected was approximately 180 mg. Soon after the injection, the patient became cyanotic, unconscious and convulsive. Necropsy showed acute passive hyperemia of various organs, but no anatomic condition that could explain the sudden death. Nupercaine was demonstrated in the fluid in the urinary bladder and also in a mixture of tissue from the liver, spleen and kidneys.

**SOAP NECROSIS OF THE PREGNANT UTERUS.** O. TILCHER, Virchows Arch. f. path. Anat. **284:817**, 1932.

Soap solution injected into the pregnant uterus is widely used among the laity of Germany to induce abortion. Runge, in 1927, described a characteristic form of necrosis of the uterus due to this procedure. Since that time a few additional cases have been reported. These are reviewed by Tilcher, who adds a case in which death occurred six days after the injection of the soap solution. The findings were the characteristic ones previously described, namely, widespread recent necrosis of the uterine wall, gelatinous thrombosis of the large venous sinuses of the placental site, marked engorgement of the vessels and hemorrhage. The area of necrosis was well delimited from the adjacent myometrium and resembled an anemic infarct. Secondary bacterial invasion of the dead tissue had occurred, but there was little or no inflammatory reaction in or about the dead tissue. The endometrium revealed only a slight change. Hemolysis was evident in the areas of hemorrhage. The adnexa of one side were similarly involved. The changes described are ascribed to the injection of the soap solu-

tion directly into the subplacental sinuses. The relative infrequency of uterine necrosis, in view of the widespread use of soap as an abortifacient, is explained by the fact that the solution must enter the venous sinuses if it is to cause necrosis. In two recorded instances, similar changes followed the injection of lysol solution and of an alkaline solution of unknown composition. The condition is of medicolegal importance, because it is so characteristic in its gross and microscopic pathology as to warrant the conclusion that abortion has been induced.

O. T. SCHULTZ.

### Technical

#### MELANOMA STUDIES: II. A SIMPLE TECHNIQUE FOR THE DOPA REACTION. GEORGE F. LAIDLAW and SOLON N. BLACKBERG, Am. J. Path. 8:491, 1932.

The authors describe a simple technic for Bloch's dioxyphenylalanine (dopa) reaction. Three stock solutions are prepared and kept in the refrigerator: (a) a 1:1,000 solution of 3, 4-dioxyphenylalanine in distilled water; (b) 11 Gm. of disodium hydrogen phosphate in 1,000 cc. of distilled water, and (c) 9 Gm. of potassium dihydrogen phosphate in 1,000 cc. of distilled water. The reagent must be slightly alkaline. Just before cutting the sections, the reagent is buffered by adding 6 cc. of the sodium phosphate and 2 cc. of the potassium phosphate solution to 25 cc. of the dioxyphenylalanine solution, giving the optimum  $pH$  of from 7.3 to 7.4. Frozen sections of fresh tissue are immersed in 5 or 10 cc. of the mixture at 37 C. for from four to six hours. At two hours and every hour thereafter a section is examined microscopically. Melanoblasts and myelogenous leukocytes blacken slowly; the rest of the tissue remains colorless. When the melanoblasts are stained sufficiently, the sections are rinsed in distilled water, dehydrated, cleared and mounted in balsam by any of the usual methods.

The reaction may be hastened either by using a higher temperature, from 58 to 80 C., or by increasing the alkalinity to 8 or even higher. Such reactions are finished in an hour or two. Rapid reactions should be controlled with the microscope every twenty minutes, for the fluid blackens quickly from the accumulation of dioxyphenylalanine-melanin, and the sections are likely to over-stain. Slow reactions give the more delicate pictures.

The tissue must be fresh. After death or excision from the living body, the reacting ferment diffuses quickly into the surrounding tissue and disappears. Fixation in a dilute solution of formaldehyde, U. S. P. (1:5) for not longer than three hours is permissible and facilitates the cutting of frozen sections. Other fixatives destroy the ferment quickly. No successful way has yet been found to preserve the tissue for a longer time than a few hours. However, after the reaction has taken place, the stain is permanent. Before staining, neither the block of tissue nor the sections should be permitted to lie in water for longer than the few seconds of a quick rinse, for water extracts the ferment quickly. The sections are dropped from the microtome knife directly into the freshly-prepared dioxyphenylalanine mixture.

An important innovation introduced by the authors is the renewal of the mixture at the end of half an hour and several times thereafter if the fluid darkens before the melanoblasts are fully stained. Renewal of the reagent extracts from the tissues any excess of acid or alkali that would interfere with the reaction and by removing the accumulated dioxyphenylalanine-melanin prevents the common fault of overstaining.

Contrary to the opinion of European workers, the authors find that surgical preparation of the skin with iodine does not interfere with the reaction. They find it to be a specific stain for melanoblasts and for myelogenous leukocytes. Bloch's special technic for leukocytes is described.

GEORGE F. LAIDLAW.

#### THE SILVER IMPREGNATION OF NERVE FIBERS IN PARAFFIN SECTIONS. N. C. FOOT, Am. J. Path. 8:769 and 777, 1932.

Two methods are described for impregnating nerve fibers in paraffin sections; one is a modification of the Ramón y Cajal silver nitrate block impregnation,

while the other is Rogers' technic practically unmodified. The former is best suited to the demonstration of fibers in the central nervous system and in large peripheral nerve trunks in their relation to supporting structures. The latter is an application of Rogers' method for demonstrating terminal nerve-endings for the more general purpose of bringing out nonmedullated fibrils in the central nervous system. Both methods are designed for general use in the histologic laboratory on tissue that has been fixed not over five hours post mortem. The silver nitrate method is well standardized and should produce reasonably uniform results; the Rogers method may entail a modicum of practice in the step whereby the sections are reimpregnated one by one in the diammoniacal silver; otherwise it presents no pitfalls for the unwary.

Experiments with four representative groups of fixatives, used on standard material (normal human femoral nerve), followed by a standardized, simple method of silver impregnation show that the results differ almost directly as the number of fixatives used. Although the variation within a given group of similar fixatives is slight, that between any two groups is decidedly marked. Alcohol fixation tends to remove lipins from the myelin sheath and thus affords the clearest impregnation, possibly the most veracious. The best alcoholic solution is a combination of alcohol, chloroform and acetic acid. Fixation in formaldehyde, even when neutral formaldehyde is used, causes marked distortion of the neurons and brings out a certain amount of what may be considered to be extraneous detail, caused by the coagulation or the chemical alteration of the myelin. Chromate fixation, while it affords precise and clear pictures, demonstrates even more histologic detail, which is probably artefact, owing to a similar, but more pronounced action on the lipins. Fixation in such an acid solution as Bouin's fluid causes an accentuation of the connective tissue elements at the expense of the nervous elements and gives to the neurons an unduly swollen and transparent appearance without effecting much metachromatic contrast.

## AUTHOR'S SUMMARIES.

SILVER IMPREGNATION OF GLIA AND NERVE FIBERS IN PARAFFIN SECTIONS AFTER FORMALIN FIXATION. H. C. WILDER, *Am. J. Path.* **8**:785, 1932.

Ganglion cells, nerve fibers, glia cells and their processes are black. Tissues fixed twenty-four hours after death or after removal show excellent impregnation of nerve fibers and fibrous astrocytes, but the processes of protoplasmic astrocytes and oligodendroglia cannot be demonstrated when more than six hours have elapsed before fixation. In tissue fixed when fresh all the fibers are sharply defined, but when fixation is less prompt the fibers tend to become granular. Although differentiation between nerve fibers and glia must be on a morphologic basis, the method has the advantage of being quick, simple and applicable to paraffin sections of formaldehyde-fixed tissue.

## AUTHOR'S SUMMARY.

THE WASSERMANN REACTION AND CERTAIN PRECIPITATION REACTIONS. HEINRICH SCHMID, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **75**:381, 1932.

The report is a comparative study of the classic Wassermann reaction with cholesterolized beef heart extracts, and of the Sachs-Georgi, the citochol and the Kahn reactions. The greatest specificity is demonstrated by the Wassermann reaction; the greatest sensitivity, by the Kahn test. The Sachs-Georgi test was abandoned owing to lack of sensitivity. The best results were obtained by the employment of the citochol and Kahn reactions alongside of the Wassermann test. Schmid considers the Kahn test as the best of all precipitation tests.

## I. DAVIDSOHN.

## Society Transactions

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### PATHOLOGICAL SOCIETY OF PHILADELPHIA

*Regular Meeting, Nov. 10, 1932*

V. H. Moon, *President, in the Chair*

#### DEVELOPMENT OF A PATHOLOGIC LABORATORY IN THE PHILADELPHIA GENERAL HOSPITAL. J. H. CLARK.

The important events in the development of a pathologic laboratory as an organized unit of the Philadelphia General Hospital may be summarized as follows:

1. The rule in the "Rules and Regulations of the Internal Government of the Almshouse and House of Employment" of January, 1822, requiring the preservation "of at least two anatomical preparations by each resident medical student" and the preservation of specimens removed at operation "if deemed necessary" by the surgeon.
2. The recommendation by the Medical Board of the Almshouse and Hospital, in 1828, that provision be made "for a room for a laboratory (fireproof), and dead-room, and another for post-mortem examinations," in the new buildings to be erected in Blockley township.
3. The motions, made at the meeting of the Medical Board in 1860, by J. L. Ludlow, secretary, that a museum be instituted and that D. Hayes Agnew be appointed curator. Both motions passed.
4. The erection, in 1860 and 1861, of a new clinic building, which housed not only the museum, but a laboratory, a morgue and an autopsy room.
5. The appointment of James Tyson as microscopist to the hospital in 1866, and the purchasing of a microscope (value \$250.00) in 1867.
6. The appointment of William Pepper as curator of the museum in 1867. In September of that year, he began the series of postmortem examinations which has been continued unbroken to the present time (25,000).
7. The appointment of James Tyson as the first official pathologist (so designated) in 1871, and the publication by him, with R. M. Bertolet, in 1874, of the first catalog of the museum, which listed 322 specimens.
8. The erection of a separate building for the laboratory, morgue and autopsy room in 1885 and 1886, and of a building for the museum adjacent to it in 1890.
9. The appointment of E. O. Shakespeare as the first official bacteriologist (so designated) in 1889.
10. The combining of all laboratory activities under one directing head in 1903 by the appointment of Randle C. Rosenberger as "Director of Clinical Laboratory." Prior to this time simple routine laboratory procedures had been done in rooms attached to the wards. Now all laboratory work was done in the laboratory building, and its scope was increased tremendously.
11. The appointment by the Medical Board, in 1913, of a "Reorganization Committee" to procure money from the city council for the erection of a new, modern Philadelphia General Hospital, which began with the completion of the Pathological Laboratory Building in 1919, under the direction of E. B. Krumbhaar.

In this way there has grown out of the individual initiative and interest of certain men an organized laboratory under one directing head, composed of seven subdivisions, each with its own chief and assistants in the following fields: (1) pathology, both gross anatomy (postmortem examinations) and histopathology; (2) clinical pathology; (3) bacteriology and serology; (4) biochemistry; (5)

neuropathology; (6) photography and museum; (7) library and records. The laboratory building also houses the Division of Radium Research, which has its own director.

Certain members of the hospital staff, who fostered interest in pathology by their efforts and gained prominence because of their writings, stand out as playing an important rôle in this development. They are: Benjamin Rush, author of many essays and books; W. C. Horner, anatomist and histologist; Samuel Jackson, author of "The Principles of Medicine Founded on the Structure and Function of the Animal Organism" (1832); Robley Dunglison, author of "Human Physiology," "A Dictionary of Medical Science" and other publications, and William W. Gerhard, who differentiated typhus from typhoid (1836) and wrote "On the Diagnosis of Diseases of the Chest" (1836).

The men of a later period who were instrumental in helping to organize a laboratory were J. L. Ludlow and Roland G. Curtin, both of whom served as chief of staff.

David Riesman, now chairman of the Medical Board, as chairman of the Reorganization Committee was instrumental in securing the assistance of the city officials in the erection of the new Philadelphia General Hospital, which has just been completed.

#### ORIGIN OF MEGAKARYOCYTES IN EXTRAMEDULLARY LOCI. R. P. CUSTER.

In the course of experiments to determine the effect of "reticulo-endothelial blockade" on the development of myeloid metaplasia in rabbits with long-standing anemia and with infection, megakaryocytes appeared in great numbers in the spleen, liver and lymph nodes of one animal. The bone marrow was extremely degenerated, and the organs mentioned had assumed the burden of blood formation in toto. Another animal, similarly treated with sapotoxin and particulate matter for the same period (nine weeks), showed an intact, active marrow, considerably less erythropoiesis and granulopoiesis in the viscera and practically no megakaryocytic metaplasia. In none of the animals that were vitally stained did complete "blockade" of the reticulo-endothelial system occur, hyperplasia of these elements occurring with sufficient rapidity that many nonpigmented cells were present at all times.

The bone marrow giant cells in the animal mentioned first were seen in splenic sinusoids and pulp, in hepatic sinusoids and extravascularly between cords of hepatic cells, and in pulp and lymph sinuses of the nodes; an occasional megakaryocyte was seen in the lung, but none in other organs of the general circulation. (Blood smears during life showed occasional megakaryocytic fragments and naked nuclei.) All evidence pointed toward these cells being autochthonous in their foreign situation, rather than embolic from the bone marrow. The cells were seen in all stages of development from blastic to degeneration forms. They appeared to arise from endothelial elements of the reticulo-endothelial system, budding into sinusoidal lumens, and from the cells of the general reticulum. They arose in two fashions, first through formation of a multinucleated syncytium, and second through hypertrophy and nuclear multiformity of mononuclear derivatives of both reticular and sinusoidal-endothelial cells. Many paired cells, one degenerating, one regenerating, gave the impression that stimulus to new formation was furnished by a hypothetic "Nekro-hormone."

This paper will be published in full in *Virchows Archiv für pathologische Anatomie und Physiologie und für klinische Medizin*.

#### POLIOMYELITIS. N. W. WINKELMAN.

The mechanism of the development of poliomyelitis has been the subject of a great deal of study and controversy, and at the present time is still far from being settled. Landsteiner and Popper are given credit for being the first to repro-

duce indisputable poliomyelitis. They introduced a piece of the spinal cord of a boy who had died of acute poliomyelitis into the peritoneal cavity of a monkey. The disease produced was characterized by paralysis and the histologic changes of acute poliomyelitis. These results have been corroborated by numerous writers. Similar experiments were carried out on other animals, but no consistent results were obtained. Flexner and Lewis failed to cause the disease in guinea-pigs, rabbits, horses, calves, pigs, rats, mice, dogs and cats. Other observers have found only the monkey susceptible. In view of the fact that the virus that produces poliomyelitis is not an ordinary bacterium, because it is ultramicroscopic, passes through a Berkefeld filter and is resistant to glycerin, the method by which the organism gains entrance to the body is still much in dispute. Experimental work along this line has resulted in rather interesting findings. Four diseases are known today which experimentally produce similar histologic pictures in the central nervous system. These are rabies, epidemic encephalitis, poliomyelitis and Borna disease, which apparently occurs only in horses. The analogy of poliomyelitis to rabies is remarkable. It has been known for a long time that the spread of the virus in rabies occurs by way of the nerves. Homen was able to trace the course of lymphatics along the nerves. While poliomyelitis can be produced experimentally by injection anywhere in the body, the most reliable methods are those involving intracerebral and intraneuronal inoculations. Leiner and Wiesner felt that they observed a definite relation between the site of inoculation and the site of paralysis analogous to that observed in tetanus. Flexner and Lewis and others demonstrated that the inoculated extremity is the first to become affected with the disease. Wickham claimed that almost invariably inoculation in a nerve of a posterior extremity produced paralysis which was situated in and tended to remain restricted to the hind end of the body. Infection through the digestive tract caused paralysis of the posterior part of the body and of the respiratory tract. Other results indicate that the site of the paralysis depends on the site of the inoculation and that the virus of poliomyelitis reaches the spinal cord by the shortest route. This would further tend to prove that the organism travels along the nerves by way of the accompanying lymphatics. Leiner and Wiesner clamped the sciatic nerve of an animal and injected the virus into the nerve distal to the clamp; poliomyelitis did not develop. Burrows felt that he had evidence that the infection goes by way of the intra-intestinal lymphatics and then through lymphatic structures of the abdomen. The work of Seifried and Spatz is interesting. They too believe that the virus of poliomyelitis reaches the central nervous system through the lymphatics to the spinal fluid, and that the spinal cord and brain stem are involved as a direct result of the infection of the spinal fluid. They think that other theories of the spread of the virus "*auf dem Liquorweg*" have certain flaws. The first serious objection to their point of view that the injected virus goes through the spinal fluid is that the subarachnoid space is usually free from severe inflammatory reactions. They feel, however, that at times the organisms invade a tissue by a point of dissemination without producing an inflammatory reaction in the tissue itself. Another objection is the frequent invasion of the *Rautenhirn* (rhombencephalon). They feel that additional factors must be called into being to explain this invasion. They believe that the basal meninges are invaded in one of two ways: first, through the meningeal blood vessels, and second, through the perineurial lymphatics which have a connection with the subarachnoid space. The spread of the virus along the nerves has been shown by Schaffer and others in rabies and by Zwick and his co-worker in Borna disease.

In the study of any typical case, one is struck by the selective action of the virus of poliomyelitis. If it is true that the virus gains entrance to the spinal cord by way of the peripheral nerves along its lymphatics, one can easily explain the rather isolated involvement of the gray matter, particularly that in the anterior horns. The blood supply through the anterior spinal artery is insufficient to explain the spread by this inflammatory process. In the microscopic examination of preparations from cases of poliomyelitis, I have been struck with the fact that

the inflammatory process and the degeneration of the motor cells in the anterior horns seem to be in relation to the entrance, or rather exit, of nerve fibers from the ganglion cells. There seems to be a grouping of the inflammatory reaction in small islands opening up, as it were, out of a clump of nerve fibers. At this point it is possible that the virus which comes along the nerve roots goes to its destination in the anterior horns before being liberated, and it is probably for this reason that it punctures the subarachnoid space without producing in it a reactive inflammation. This would explain the limitation of the inflammatory reaction to the gray matter. It would explain the gradual involvement of the anterior horns because of the affinity of the virus for motor nerves. It would also explain the lesser involvement of the posterior horns, because probably some of the virus does go up the posterior roots into the spinal cord.

The fact that there is practically no reaction in the subarachnoid space points the way for rational treatment, since the virus is probably not present in this space. Intravascular injection is the method of choice although the treatment is of no avail if the virus reaches the spinal cord before the latter is prepared to combat the infection. The conditions related to poliomyelitis are in definite contrast to those which are blood-borne. The latter group includes paresis, encephalomyelitis disseminata and probably also so-called acute multiple sclerosis and the form of encephalitis which is due to metastatic lesions in the brain from an ulcerated endocarditis.

#### A CASE OF CONGENITAL CARDIAC ANOMALY. EMMA BEVAN.

A case of congenital cardiac anomaly that does not fit into the usual pictures occurred in a Negro boy who died four days after birth. The mother was a quartipara, whose pregnancies had occurred close together; she had been married six years. She gave a negative Wassermann reaction.

The infant's heart weighed 50 Gm.; it measured 5 cm. across the base and 7 cm. from the base to the apex. The wall of the right ventricle averaged 6 mm. in thickness; that of the left ventricle, 4 mm. Both ventricles were seen on the ventral surface. The left auricle was large and lay above and medial to the left ventricle; the right auricle was small. When the heart was opened, the chambers of the left auricle and of both ventricles were large. The foramen ovale was patent. The right auricle and ventricle communicated normally through the tricuspid ring, which was normal. The left auricle communicated with both ventricles through a septal defect, just below the pulmonary ring. A defect in the upper part of the interventricular septum allowed communication between the ventricles; this orifice, however, was guarded by a mitral valve the chordae tendineae of which sprang from papillary muscles in the left ventricle. There was inversion of the position of the left auricle and ventricle with the aortic ring to the left of the mitral valve. The superior and inferior venae cavae and the coronary veins opened into the left auricle; the pulmonary veins emptied into the right auricle. Both coronary arteries arose above leaflets of the pulmonary artery, which did not communicate with the lungs but gave rise to the innominate, left common carotid and left subclavian arteries. The systemic aorta showed definite atresia just proximal to the orifice of the patent ductus arteriosus; proximal to the stenosis, it gave off two pulmonary arteries at the arch. The aorta descended normally.

The brain showed an enormous dilatation of the artery of the left sylvian fissure, with many interlacing vessels; this mass had compressed the prerolandic and postrolandic convolutions. The vessels of the right sylvian fissure were dilated and showed mild tortuosity.

The anomaly depended probably on a defect of torsion associated with a misdirection of the septum aorticum. The case is presented as one of atypical mirrored situs inversus. The association of mongolian idiocy and other mental deficiencies with congenital heart disease is reflected in this case through intracranial vascular changes with compression of the brain.

Regular Meeting, Dec. 8, 1932

V. H. Moon, President, in the Chair

THE ANNUAL GROSS LECTURE: THE INFLAMMATORY REACTION IN TUBERCULOSIS. ESMOND R. LONG.

The acute inflammatory response to tuberculous infection varies greatly in different species of animals. Its intensity does not correspond directly with the resistance of the species to the disease. In certain animals of low resistance an intense initial cellular response occurs, and in others with high resistance the initial response is slight. In other comparisons no correlation can be observed. Factors other than the success or failure of inflammatory suppression play a part in determining the fate of the infecting agent.

Within an animal species the intensity of response to tubercle bacilli may vary widely, the chief modifying factor being the hypersensitivity conferred by previous inoculation with this micro-organism. Not all susceptible animals acquire hypersensitivity. In the hypersensitive animal the inflammatory reaction to tubercle bacilli develops with greater speed and is of greater intensity. Otherwise the reaction is similar to that of a first infection. Many cells are affected in the hypersensitive state, including the vascular endothelium and the various types of leukocytes.

The inflammatory reactions of tuberculosis can be reproduced by the use of pure substances extracted from the body of the tubercle bacillus. Chronic productive inflammation is caused by certain lipoids of the tubercle bacillus, and acute exudative inflammation, similar to acute tuberculosis in man, is caused in the hypersensitive animal by a protein of the tubercle bacillus and by some of its derivatives.

The first cells responding to the injection of tubercle bacilli are the polymorphonuclear leukocytes. They rapidly engulf and localize the bacilli, thereby determining the site of tubercle formation. Within twenty-four hours the polymorphonuclears are phagocytosed and destroyed by large mononuclear cells, which complete the development of the tubercle.

The source of the mononuclear cells is still in dispute. It appears to vary in different organs. In the liver and in the lungs a high percentage of the mononuclear cells of developing tubercles arise from previously fixed phagocytic cells (Kupffer cells and alveolar phagocytes). In the omentum, primitive cells apparently identical with the monocytes of the blood give rise to epithelioid cells. In all of these locations, however, mononuclears from the blood take some part in tubercle formation.

The part played by the mononuclears of the blood is well shown in the cornea. When this normally avascular organ (rabbit, guinea-pig, cat) is infected with tubercle bacilli, the site of infection, although rapidly permeated by polymorphonuclears, is not invaded by mononuclears until new blood vessels approach. The new capillaries are seen to be surrounded by collars of large mononuclear leukocytes. Among these, mitotic figures are very rare. Figures of migration from the vascular lumens are fairly common, and large mononuclears, in considerable excess over the quantity normally found in the blood, can be seen in small vessels. The mononuclears, which thus appear to come largely from the blood stream, wander away from the walls of the blood vessels and by hypertrophy and change in structure, without division, become epithelioid cells.

The distinctive cytoplasmic state of the epithelioid cells appears to be the result of destruction of many tubercle bacilli and progressive emulsification of their lipoids.

This paper will be published in full in the *American Journal of Medical Sciences*.

## NEW YORK PATHOLOGICAL SOCIETY

*Regular Meeting, Dec. 22, 1932*PAUL KLEMPERER, *President, in the Chair*

## CONTACT CARCINOMAS OF THE STOMACH. CHARLES T. OLcott.

A stomach was removed by Dr. Seward Erdman from an Italian man, aged 42, who had been ill for three months. On the posterior surface there was a firm, bosslike elevation 4 by 3 cm. in diameter, elevated 1.8 cm. above the serosa. This was found to be an ulcerated carcinomatous mass with undermined edges. The surrounding wall was apparently intact except for superficial ulceration. On the anterior surface of the stomach there was a firm area, the mucosa of which showed another ulcerated carcinomatous mass. This was 3 by 1.5 cm. in diameter. It lay in such a position that it had apparently been in contact with the first tumor across the intervening gastric lumen. A normal-appearing mucosa and wall separated the two tumors. Histologic preparations of both growths showed anaplastic carcinoma. The process was thought to represent carcinoma spreading by contact, though the possibility of lymphatic spread or even of a multicentric origin was considered. Ten months after operation, the patient was alive but showed apparent metastases to the vertebrae.

## COMPARATIVE ANATOMY OF THE SEMILUNAR CARTILAGES OF THE KNEE: NORMAL PRESENCE OF BONE IN THE MENISCI OF SOME ANIMALS. HENRY L. JAFFE.

In man the meniscus of the knee is divided into an inner avascular and an outer vascular portion. The avascular portion is more or less tendinous and contains some encapsulated cells, which gives the structure the appearance of fibrocartilage. The menisci are more or less pearly white at birth; early in life, however, even before puberty, they often undergo changes in color, becoming yellowish or yellowish brown, and in advanced age they may appear brownish. These changes in color are associated with a progressive degeneration within the substance. Sometimes calcium is deposited in the degenerated ground-substance, and in rare instances quantities of cartilage are deposited, which leads to striking gross calcification and even permits the roentgenologic visualization of the menisci. Ossification of the degenerated calcified semilunar cartilages occurs rarely; in fact, only one or two instances have been recorded. In a large experience I have never seen the phenomenon.

In the rat, mouse and guinea-pig, the menisci after birth become cartilaginous and later, in the anterior half, undergo ossification by direct bony metaplasia of the cartilage. Lymphoid marrow appears between the bony trabeculae. As the animal becomes older, the bone becomes more mature and more lamellar.

The presence of bone normally within the menisci of these animals seems not to be known. Investigation of the available literature in the library of the New York Academy of Medicine, in the Museum of Natural History and in the zoologic and biologic libraries of Columbia University yielded only one reference to this occurrence. That was a note by Retterer (*Compt. rend. Soc. de biol.* **58**:44, 1905) which seems to have been completely lost sight of; he also noted bone in the menisci of the guinea-pig and the rat.

## DISCUSSION

PAUL KLEMPERER: Am I correct in thinking that the semilunar cartilage in man is not vascularized, or does it show blood vessels?

HENRY L. JAFFE: The semilunar cartilage in man is divided into two portions, an inner one that is not vascularized and an outer vascular portion. The inner avascular portion corresponds in structure more with the posterior portion of the cartilage, as seen, for instance, in the guinea-pig.

PAUL KLEMPERER: There is, then, no difference in the vascularization in the human being and in the guinea-pig. Does semilunar cartilage regenerate from small particles which are left? That is a practical question.

HENRY L. JAFFE: There have been a number of observations recently, particularly by surgeons who had removed the semilunar cartilages, or thought that they had removed them. The patients came back later because of some other condition in the knee, and sections of tissue showed semilunar cartilage. Apparently the cartilage can regenerate if small fragments are left, or the connective tissue in the knee may in some way anatomically reconstruct something that resembles semilunar cartilage.

A CASE OF MONILIASIS WITH MENINGEAL INVOLVEMENT. LAWRENCE W. SMITH and MACHTELD E. SANO (by invitation).

A case of moniliasis occurred in a white boy 22 months of age. The child was sick at home for two weeks before admission to the hospital. When first



Fig. 1.—Section of lung showing marked areas of peribronchial thickening and areas of bronchopneumonia.

seen he had a profuse, white, patchy membrane covering the buccal mucosa and the hard and soft palates and extending down the pharynx. He was in acute respiratory distress, which was relieved by laryngeal suction with the removal of membrane. The membrane was found to be made up chiefly of the growth of a monilia, fibrin and leukocytes. He had complicating bronchopneumonia, which persisted until his death eleven days later. Because of vague reflex disturbances, a lumbar puncture was done, and after forty-eight hours, a growth of the monilia was obtained. Bilateral otitis media developed, and terminally a convulsion, but at no time during the course of the disease were meningeal symptoms prominent.

At autopsy there were marked rachitic nutritional skeletal changes. The positive pathologic changes of significance were felt to be chiefly in the respiratory tract and in the central nervous system. The lungs showed a subacute inflammatory process, chiefly bronchial, with marked peribronchial thickening and secondary bronchopneumonia. Several other patchy areas of definite grayish consolidation were seen, and microscopically the monilia could be readily demonstrated in the exudate, which was notably mononuclear. In the gastro-intestinal tract, there was

moderate congestion as well as considerable adherent gelatinous material which on culture yielded a growth of the same monilia. When the skull was opened, the dura was found to be tense. Reflection exposed a thick, whitish, gelatinous exudate which was most marked at the base of the brain. Cultures and sections showed the monilia in the exudate. The monilia was also obtained from cultures of the blood from the heart and from both ears, but these cultures showed in addition a terminal hemolytic streptococcal infection.

In view of the unusual nature of the case, it was felt that every effort should be made to identify the organism. Control strains were obtained from Dr. Benham of Columbia University and from the National Institute of Health at Washington, D. C.

Inoculation of animals with the various strains was made to determine pathogenicity and also subsequently to develop specific serums for absorption tests. The pathogenicity of our strain was much more marked than that of the others. Of course, it was more recently isolated and might lose this feature in time.

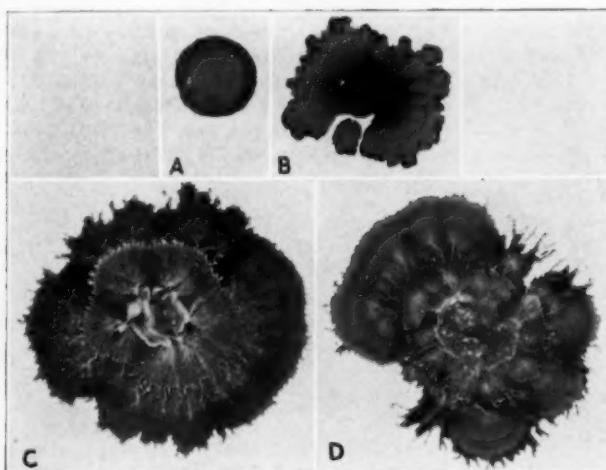


Fig. 2.—Cultures on corn-meal agar: *A*, strain 202, *M. psilosis*; *B*, strain 894 (Benham), *M. albicans* from sprue; *C*, strain 457 (Benham), *M. albicans* from thrush; *D*, strain 636, *M. albicans* (?).

Curiously, it had an almost regular predilection for localizing in the central nervous system and producing meningitis or multiple abscesses of the brain, usually of the right side of the cerebellum. Involvement of the brain by the control strains was observed rarely. The characteristic pathologic process caused by all strains was the formation of multiple abscesses, always of the kidney, usually of the lung and the heart, and often of other organs. The spleen apparently is never involved.

Culturally, the best medium for differentiation was found to be corn-meal agar, as only slight differences could be noted on the usual Sabouraud's medium. These points of difference or of similarity are best shown by the cultures presented in figure 2, in which the curious tuftlike appearance of the periphery of the colony can be readily seen. Morphologically, the colony can be identified as that of a monilia by its budding and mycelial forms as well as by its spores and chlamydospores. The fermentation reactions were more nearly those of Stovall and Dubolz type II, except that milk was not coagulated, or those of Benham's M 6 type. Absorption tests were not particularly satisfactory, but as a whole seemed to place the organism as an atypical one more nearly approaching *Monilia albicans* than any other.

## DISCUSSION

CHARLES J. SUTRO: Some time ago one of my associates performed an autopsy in a case of thrush. He scratched his finger with an infected knife. A severe infection of the finger developed, with marked infiltration of the soft tissue. Two days after the onset he cultured the pus and found a monilia in pure culture similar to the type found in the patient's mouth. He has fully recovered. This incident shows that monilias may produce local infection by direct contact.

J. GARDNER HOPKINS: I believe this to be the first case of monilia meningitis reported under the correct name, though I do not believe that it is the first case reported. After reading the descriptions of some cases recorded as instances of blastomycosis or torulosis, one suggests that the condition was moniliasis. I have been particularly interested in a case that Evans and Ball reported in *California and Western Medicine*, I think under the title of "Torula Meningitis." From looking at the picture of their culture one would be fairly sure that the organism was a monilia, though one could hardly be sure of the type. I judge from the bacteriologic report of Dr. Smith and his co-worker that they considered this organism as probably more closely related to *M. albicans* than to other monilias. It is fortunate that they did not emphasize the slight variations too much, because the tendency to slap a new name on a fungus which has one more bud than another has made the obtaining of accurate information from the reports of such cases difficult. The complexity of the nomenclature has not prevented the reporting of cases due to different fungi under one name and the classification as torula meningitis of conditions which were really monilia meningitis. The distinction between these two forms of meningitis is real.

The most interesting point is why, in such a common infection as moniliasis, there is one case of extensive general infection with involvement of the lungs and meninges, whereas ordinarily the condition is relatively benign. This suggests that the organism may be of a somewhat different species, which will have to be decided later. An important point, however, was brought out in the clinical history, namely, that the patient was rachitic. This suggests that the nutritional condition is important in infection of this type.

LAWRENCE W. SMITH: Experimental infection of the skin, especially in relation to the nails, has recently been reported. Monilias apparently produce mild, subacute lesions which heal spontaneously in from one to three weeks.

I had one other case of generalized moniliasis, though not involving the central nervous system, in an infant in the Boston Floating Hospital a number of years ago. The condition started as typical thrush spreading over the face and scalp and appearing also around the anal orifice and extending over the buttocks and genitalia. At autopsy there were generalized metastases in all the viscera, but no lesions of the brain.

Dr. Hopkins' comment regarding the importance of the nutritional state in such infections is extremely pertinent. I became interested in infections with monilias about ten years ago, in relation to a number of cases of sprue which I observed, and I too tried experimentally to find out the relationship of the organism to the disease. When normal guinea-pigs were fed almost incalculable amount of monilias, lesions of the gastro-intestinal tract occurred only occasionally, but when animals which had been fed a vitamin-deficient diet and which were in a state of mild or latent scurvy were fed monilias, ulcerative lesions of the intestinal tract were produced almost regularly. I think that this point should be stressed in relation to infections by organisms of this general type, ordinarily probably nonpathogenic, but under suitable circumstances harmful.

## MYELOID LEUKEMIA WITH OSTEOSCLEROSIS. SHELDON A. JACOBSON.

L. K., a man, aged 28, a research chemist, whose past history was unimportant, had been engaged in investigations involving the use of pyridine and aniline dyes. Pain in the left thigh became noticeable. This spread to the right thigh and the lower part of the back, gradually increasing, and progressive weakness developed. The patient entered the hospital on development of the pain in the left thigh and

remained for six weeks. During this time he showed marked anemia, aleukemia (a white blood cell count as low as 1,000) and persistent abnormalities in the blood smear (anisocytosis, reticulocytes, nucleated red cells, myelocytes and myeloblasts to the extent, at one time, of 35 per cent). He became gradually weaker, and died a month after discharge.

The anatomic diagnosis was: chronic myelogenous leukemia; anemia; leukemic nodules in the liver, spleen, kidneys and testes; hepatomegaly and splenomegaly; lymphoma of all intra-abdominal nodes; dilatation of the heart; pulmonary edema; petechiae in the skin, right bronchus, epicardium, stomach, intestine, renal pelvis and bladder; osteosclerosis of the vertebrae, femur, skull, ribs and patella.

The osteosclerosis was an unexpected finding. In spongy bone, it manifested itself in a thickening of the trabeculae; in the long bones, in a thickening of the cortices with narrowing of the marrow space. The vertebral lesion was minimal in the cervical region, increasing toward the sacrum.

Some of the haversian canals of the femur were widened and filled with tumor tissue. Many had been narrowed almost to the point of obliteration, displaying several concentric cement lines. Extensive areas of the bone were more or less completely necrotic. In contrast to cases previously described, there was periosteal bone formation by the ribs, calvarium and femur. Extensive areas of marrow, particularly in the femur, were necrotic; some were hemorrhagic or in an early stage of loose fibrous regeneration. Most of the marrow, however, was leukemoid.

#### DISCUSSION

**HENRY L. JAFFE:** It is interesting to emphasize the considerable amount of aseptic necrosis that was present owing to the reduction in the vascularization of the bone. Dr. Richter and I did some work about four or five years ago, some of the results of which have been published, which may be worth citing. We transplanted into the tibial marrow cavity of the guinea-pig a number of tissues, thymus gland, lymph node, spleen, muscle, cartilage and bone. We tried to ascertain the reaction of the bone and marrow to these substances. The responses were curious. Some writers hold that the small cells of the thymus are lymphoid, and that the thymus is really a lymphoid organ. When thymic tissue was introduced into the marrow cavity of the tibia of the guinea-pig, it acted like a foreign body; it rapidly became encapsulated and surrounded by bone, which interfered with the circulation, and finally it underwent rapid involution or atrophy. When lymphoid tissue in the form of a lymph node was introduced, it was not encapsulated, but within a few months, it disappeared gradually. There was complete merging. When we introduced tissue from the spleen, we obtained a reaction between those produced by the lymph node and by the thymus. The splenic tissue was more in harmony with the marrow than was the thymic tissue, and certainly less so than the lymph node. I do not know that this has any particular reference to the sclerotic response in leukemia, but certainly it gave us some suggestive ideas as to the interrelationship between bone marrow and these other organs and tissues.

**M. A. GOLDZIEHER:** In discussing the relationship between osteosclerosis and leukemia, it would be a great mistake to summarize all the cases under the heading of osteosclerosis following leukemia. There have been cases in which the osteosclerosis was observed first, and was followed by development of the leukemic changes. In the majority of cases, however, it seems that the osteosclerosis develops in the course of the leukemic process. This brings me to the discussion of another phenomenon which I think is closely allied to it, and which I have recently observed in a classic case. I have reference to changes occurring in lymphosarcoma, a condition which is perhaps more closely allied to leukemia than was thought hitherto. This case of lymphosarcoma of the mediastinum also involved the lymph nodes of the abdomen and the retroperitoneal tissue. In removing the intestinal tract my associates and I found a large number of nodules scattered over the serosa. They looked almost like miliary tubercles; yet they consisted of hyaline connective tissue, placed on top of the intestinal surface but penetrating in places into the muscularis. We could not interpret these findings until we saw that in a few places the hyaline connective tissue was interspersed with lymphocyte-

like cells. Examination of the tumor tissue in the mediastinum showed all stages between typical lymphosarcoma and a completely hyaline acellular tissue. In other words, what we found could be interpreted as a tendency to heal by scarring. The same tendency might be suspected in some cases of leukemia with this particular type of pathologic process of the bones as its product. It is difficult to prove that osteosclerosis represents transformation of newly formed leukemic tissue into bone tissue. Some workers may think that osteosclerosis is rather the reaction of the endosteal tissue to irritation by the leukemic growth, but this interpretation is equally open to question. It would seem to me, however, that the occurrence in lymphosarcoma of sclerotic changes of the type described suggests the assumption of an analogous process in the leukemic bone marrow as the most likely explanation of osteosclerosis in leukemia.

CHARLES J. SUTRO: This case has an important medicolegal aspect, in that the patient worked for sometime in a laboratory in which he came in contact with aniline. The aniline intoxication probably transformed the leukemic stage to the aleukemic one, producing a temporary cure. When he was admitted to the hospital he presented the clinical picture of aplastic anemia. However, examination of the peripheral blood showed a marked increase in the nucleated red cells and myeloblasts, which gave a clue to the fact that he probably had aleukemic leukemia. There might have been some secondary regeneration, perhaps producing a marked irritative process, stimulating osseous sclerosis.

PAUL KLEMPERER: I observed similar changes in one case in which I called the condition not osteosclerosis but osteofibrosis. The changes occurred in the course of leukemia which had been treated for a considerable length of time with radiotherapy. In this instance, one could regard the process in the bones as a transition stage between fibrosis and final osteosclerosis, as the fibrosis in some places showed metaplastic bone formation. Dr. Jacobson, I think, showed fibrosis in one picture, which indicates that the sclerosis and new bone formation in his case also possibly began with fibrosis.

SHELDON A. JACOBSON: The point raised by Dr. Goldzieher as to the possibility of the osteosclerosis existing prior to the development of the leukemia is well made. Those who consider leukemia as the cause of the lesions in the bones naturally answer that leukemia may exist for a long time before one is able to detect it clinically. Moreover, a capable hematologist will detect it long before another with less experience, and naturally it may exist for some time before it is detectable. Many others regard osteosclerosis in connection with leukemia as a healing process. That also is a theory which may or may not be true.

The fibrosis in this case was not sufficiently general in its distribution to suggest that it was the intermediary stage that led to new bone formation, although that may have been the case. Bone formation was certainly not rapid, because nowhere were there cuboidal osteoblasts; they were flat even in the areas of greatest sclerosis. Furthermore, most of the areas of fibrous marrow showed necrosis of the trabeculae.

I might make another comment in connection with the point which Dr. Sutro raised concerning the aniline dyes. The man had worked until soon before coming to the hospital, and on admission he had aleukemia which may have been caused by the dyes. During the time that he was in the hospital, and during the time between his discharge and death, he was not subjected to the action of the dyes. Although he was not seen at the hospital after his discharge, autopsy showed that the blood was no longer aleukemic in type; the white cells had increased in number until they were almost comparable with the red cells.

#### MULTIPLE HEMANGIOBLASTOMAS OF THE SPINAL CORD WITH SYRINGOMYELIA AND CYSTS OF THE PANCREAS AND KIDNEY (LINDAU'S DISEASE). ABNER WOLF AND SIGMUND L. WILENS.

In 1926, Lindau described a syndrome which he named "angiomatosis of the central nervous system." Cystic or solid hemangioblastomas of the cerebellum, stem and cord, single or multiple, were found associated with angiomatosis of the

retinae (von Hippel's disease) and concomitant malformations or tumors in the somatic organs. The latter were described as cystic pancreas, cystic kidneys, hypernephromas and adenomas of the kidneys and suprarenals, and cavernomas of the liver. Lindau described fifteen cases. Ten were culled from the literature and had been variously described and classified. Five were his own. He showed that there was a distinct familial incidence, and that the average age of onset was about 30. In four of the fifteen cases, hemangioblastomas of the cord were present. In all four, the tumors were multiple, and in three they were associated with lesions of the type described outside the nervous system. In only one was there associated syringomyelia of the cord. Since Lindau's report, four more cases of multiple hemangioblastomas of the cord have been described. Three were associated with syringomyelia, and only two of these were associated with Lindau's syndrome. Thus there have been up to the present time only three reports of cases of Lindau's disease in which multiple hemangioblastomas of the cord were associated with syringomyelia.

This report presents the fourth case of this condition.

E. W., a man, aged 33, was admitted to the service of Dr. Walter Palmer in the Presbyterian Hospital, complaining of numbness in the arms and legs and gripping pains in the abdomen.

His father had died of tumor of the brain at the age of 36, and his mother, of "spinal meningitis." A twin brother and sister had died at birth.

Twelve years prior to his admission to the hospital, the patient had struck his head while diving and was unconscious for a short time. Detachment of his right retina occurred, and after twelve operations, his right eye was enucleated six years later. Two years later, detachment of the left retina occurred, and that eye was enucleated. This was unassociated with trauma.

During the year before his admission, cerebellar symptoms developed on the right side, as well as unsteadiness and a tendency to fall to the right and symptoms of syringomyelia. There were dissociated losses in sensation, from the cervical to the lumbar cord. The spinal fluid was xanthochromic. The Wassermann test of the spinal fluid was positive, but that of the blood was negative. The clinical diagnoses included syphilis of the central nervous system, gumma of the cord, syringomyelia and intramedullary tumor of the cord. The patient died of terminal lobular pneumonia.

At autopsy, we found a small cystic hemangioblastoma situated in the posterior portion of the white matter of the right cerebellar lobe, three hemangioblastomas of the spinal cord, extensive syringomyelia, cysts of the pancreas and kidneys, a cystic adenoma of the right kidney, a suprarenal rest in a retroperitoneal lymph node, a patent foramen ovale and a paraganglioma of the left suprarenal. The last mentioned condition has not previously been described in Lindau's syndrome.

Unfortunately we have been unable to obtain any specimens from the enucleated eyes or any clinical facts on pathologic reports beyond the information that they were enucleated for detached retina with terminal glaucoma. Almost all cases of angiomas of the retina end in retinal detachment, which finally necessitates enucleation. A majority of the cases of angiomas of the central nervous system are accompanied by angiomas of the retinae, and it is extremely likely that the latter condition was present.

The familial occurrence and the presence of lesions in many organs prompted Lindau to consider this condition one in which there are many congenital rests and malformations referable to one of the embryonic layers, similar in many respects to tuberosclerosis and neurofibromatosis. The embryonic layer involved in Lindau's disease was taken to be the mesoderm, and the developmental disturbance was believed to occur during the third embryonal month. At this time there occur vascularization of the retina, formation of the vascular mesodermal roof plate of the fourth ventricle, ingrowth of mesodermal elements into the pancreas and the maldevelopment leading to renal cysts.

In summary, we have presented a rare case of multiple hemangioblastomas of the cord associated with Lindau's syndrome and syringomyelia.

## Book Reviews

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**Physical Chemistry for Students of Biology and Medicine.** By David Ingersoll Hitchcock. Price, \$2.75. Pp. 182, with 26 figures. Springfield, Ill.: Charles C. Thomas, 1932.

Three fourths of Hitchcock's volume repeats in readable form and largely in mathematical terms the elements of physical chemistry. It thus allies itself with about thirty other available texts on this subject. In the remaining fourth, adsorption and the colloidal state are made bedfellows in one chapter, and membrane equilibrium and the New York concept of the lyophilic colloid in another.

According to Hitchcock, his volume is "for students of biology and medicine," a purpose hardly fulfilled, since biologic applications of physiochemical principles are merely hinted at.

Like many of his predecessors, Hitchcock therefore believes that physical chemistry can bring civilization into the biologic sciences. For this reason it is perhaps not amiss to repeat that an early and valiant band of contributors to, and forerunners of, what today goes as physical chemistry were biologists (Pfeffer, de Vries, Nägeli, Fick, Ludwig, Engelmann and others). Physical chemistry, after the work of these men, became the propagandist for the utilization of its laws in the interpretation of the phenomena of life. It has, under this head, been the mother, or the wet nurse, of certain scientific concepts, as those of osmotic pressure, electrolytic dissociation, chemical reactivity as determined by such dissociation products, catalytic action and chemical equilibrium, concepts derived, for the most part, from the study of materials dissolved in dilute form in water. When, thirty or more years ago, the physical chemists began, through advice mainly and very little through any direct experimental study of biologic problems, to insist on the validity of their laws for protoplasm, they did this, of course, on the assumption that this too was just another dilute solution. Hitchcock continues this tradition. Beginning in the nineties of the last century, one worker after another has tried to rediscover in living matter the laws of the dilute solution chemistry. We need but mention Nasse's or Hamburger's work on the osmotic pressure of cells, Dreser's or Paul's studies on the toxicity of metal salts, Kahlberg's work on the toxicity of acids and the taste of dissolved substances, Bugarszky's work on the combining value of proteins for electrolytes; Loeb's studies of ions on muscle, or Mathews' similar studies on nerves, and Waller's measurements of electrical conductance in tissues. It should now be known that none of these authors, even when on the hunt for rediscovering the laws of dilute solution of the physical chemists in protoplasm, has ever succeeded, either qualitatively or (worse) quantitatively. Protoplasm, including the blood and the lymph (but not the urine or the sweat), simply refuses to behave like a dilute solution. A lyophilic colloid system is something different. But Hitchcock makes short mention of it. There is very little mention of Hofmeister or Pauli in this volume and none of Spiro or Hardy, of Picton and Linder, of van Bemmelen, of von Weimarn or, worst of all, of Wolfgang Ostwald. At the end there is no classification of the colloids, and after vague references to older electrostatic notions of colloid stability, the new-born Donnan equilibrium ion concept of "colloid behavior," is mentioned, which any laboratory worker must find false who has ever jellied starch or iceland moss or prepared a laboratory glue of soft rubber and gasoline.

**The History of Dermatology.** By William Allen Pusey, A.M., M.D., LL.D., Professor of Dermatology (Emeritus), University of Illinois; Sometime President of the American Dermatological Association and of the American Medical Association. Price, \$3. Pp. 223, with 33 illustrations. Springfield, Ill.: Charles C. Thomas, 1933.

This is the first history of dermatology in the English language. The introduction outlines broadly the gradual development of this branch of medicine from the first descriptions of diseases of the skin in the earliest Egyptian medical records. "None of man's medical efforts can have been much earlier than those to relieve his itching and to get rid of the sores and scabs and parasites that afflicted his skin." And baldness seems to have been an urgent problem from the first. The first two chapters cover the period between 3000 B.C. and 1500 A.D. They deal with ancient Egyptian, Greek, Greek-Roman, Arabian and medieval dermatology. Many important observations were described objectively and accurately during this time. De Mondeville (1260-1320), who described the facies of leprosy in classic fashion, complained of medieval writers on diseases of the skin because "one calls serpigo what the other calls impetigo, and the third pannus, a fourth places two diseases under one species and wishes to institute only one treatment for the two, while a fifth one divides impetigo alone into three species and establishes three different methods of treatment." The next two chapters carry the reader down to the beginning of the nineteenth century, when dermatology may be said definitely to have found itself. The remaining five chapters are devoted to various epochs and phases of modern dermatology. The discussion, which is comprehensive and scholarly, centers largely on the great leaders as epitomizing the achievements of their times. Their personalities, the conditions under which they labored and the results of their labors are described lucidly and with keen insight. The dependence of advances in dermatology on advances in medical and scientific knowledge generally is set forth clearly. The illustrations are of much biographic and historical interest. At the end is a valuable historical index of dermatology. The style is clear and pleasant. The book is a significant addition to the literature on the history of medicine.

**Papers Relating to the Pituitary Body, Hypothalamus and Parasympathetic Nervous System.** By Harvey Cushing, Professor of Surgery (Emeritus), Harvard University, and Recently Surgeon-in-Chief, Peter Bent Brigham Hospital, Boston. Price, \$5. Pp. 234. Springfield, Ill.: Charles C. Thomas, 1932.

In this book are republished, with a few changes and added notes as well as illustrations, four papers on related topics, namely: (1) "Neurohypophysial Mechanisms from a Clinical Standpoint," Lister Memorial Lecture (*Lancet* **2**:119, 1930); (2) "Posterior-Pituitary Hormone and the Parasympathetic Nervous System" (*Proc. Nat. Acad. Sc.* **17**:163 and 239, 1931); (3) "The Basophil Adenomas of the Pituitary Body and Their Clinical Manifestations (Pituitary Basophilism)," (*Bull. Johns Hopkins Hosp.* **50**:137, 1932; *J. A. M. A.* **99**:281 [July 23] 1932), and (4) "Peptic Ulcer and the Interbrain" (Balfour lecture) (*Surg., Gynec. & Obst.* **55**:1, 1932). The pages and the illustrations (of great value) are numbered consecutively, and at the end is a good index. These four papers constitute a contribution of unusual importance to the study of the interpeduncular region. The main conclusion of the first paper is that "physiologically the diencephalo-hypophysial mechanism can only be properly interpreted when looked upon as a whole, and even then only when its influence on the entire organism is taken into account." In the second article significant evidence is brought forward concerning the activity of the posterior lobe of the hypophysis. The peculiar syndrome described so well in the third article as accompanying basophil pituitary adenomas "will give pathologists reason in the future more carefully to scrutinize the anterior-pituitary" for hypersecretory adenomatous lesions. The

fourth article presents "an interpretation of the neurogenic origin of peptic ulcer and an explanation of its existing prevalence." In these articles, written in characteristically fluent style, the distinguished author again reveals himself as a practical surgeon and a learned investigator, which, as he himself points out in the introduction to his Lister lecture, is indeed a rare combination.

**The American Illustrated Medical Dictionary: A Complete Dictionary of the Terms Used in Medicine, Surgery, Dentistry, Pharmacy, Chemistry, Nursing, Veterinary Science, Biology, Medical Biography, etc., with the Pronunciation, Derivation, and Definition.** By W. A. Newman Dorland, A.M., M.D., F.A.C.S., Lieut.-Colonel, M.R.C., U. S. Army. With the collaboration of E. C. L. Miller, M.D. Sixteenth edition. Fabrikoid. Price, \$7. Pp. 1,493, with 941 illustrations. Philadelphia: W. B. Saunders Company, 1932.

Many new words are defined, and new illustrations have been added. A distinctive feature of this edition is the inclusion of 279 portraits of physicians and scientists whose names are used in medical terminology. Of course this list is far from being in any sense complete. This edition, like the preceding, "has had the advantage of an exhaustive editing by the Staff of the American Medical Association, under the direction of Dr. Morris Fishbein." Another new departure is the introduction of the names for micro-organisms proposed by the committee of the American Society of Bacteriologists. It is exceptional, indeed, to run across faulty definitions or omissions. Current usage hardly justifies defining hypersensitiveness and hypersensitization as "unusual susceptibility to nonprotein substances," or the statement that "hypersusceptibility is sometimes used improperly as synonymous with anaphylaxis." The definition of granuloma inguinale and lymphogranuloma inguinale ("lymphopathia venerea") do not distinguish clearly the diseases in question. Postvaccinal and postvaccinal are defined correctly, but vaccinal is not given. Of words that should be considered for admission may be mentioned: ablastin, bacterioides, cystiphorous, onocyte, pituicyte, status varicosus and thrombocytobarin. The tables and the lists of diseases, signs, tests, operations and many other topics serve to make this a remarkably helpful book.

**Lehrbuch der Histologie und Histogenese.** By Dr. Univ. Med. Josef Schaffer, o.ö. Professor der Histologie an der Universität in Wien. Third edition. Price, 18 marks. Pp. 576, mit 640 zum Teil farbigen Abbildungen im Text und auf 14 meist lithographischen Tafeln. Leipzig: Wilhelm Engelmann, 1933.

The first edition of this book was published ten years ago. It now appears in its third edition, thoroughly revised and brought abreast with advancing knowledge. Certain parts have been rewritten completely. Seventy-one new illustrations have been added. The book is divided into two main parts: (1) the simple tissues—the blood, the epithelial tissue, the connecting and supporting substances, the muscular tissue and the nerve tissue—and (2) the special tissues or histology of the organs—the blood vascular system, the lymph vascular system, the lymph nodes, the spleen, the glands of internal secretion, the skin and its appendages, the digestive tract and its accessory glands, the respiratory tract, the urinary apparatus, the male sex organs, the female sex organs and the organs of vision, hearing and smell. The presentation is clear, succinct and orderly. The illustrations, all drawings mostly in black and white, but many in colors on inserts, are excellent. The references, arranged alphabetically according to the names of the authors, occupy thirty-two pages at the end of the book, which is well indexed. Schaffer's histology is a first class work in its field.

**Report of the Medical Research Council for the Year 1931-1932.** By the Committee of the Privy Council for Medical Research. Presented by the Lord President of the Council to Parliament by Command of His Majesty, February, 1933. Price, 2 shillings, net. Pp. 140. London: His Majesty's Stationery Office, 1933.

This report gives an instructive bird's eye view of the organization and progress of medical research in the United Kingdom, largely under governmental auspices. The first section of the report of the Medical Research Council deals with work that is receiving special attention, namely, clinical research, investigations of disorders of the nervous system, of malaria, of distemper of dogs, of the legibility of print, of maternal mortality and puerperal fever and of iodine in foodstuffs and the incidence of goiter and the studies of vitamins. Then follow sections on the National Institute for Medical Research, Hampstead, London, with farm laboratories at Mill Hill; on the work on biologic standards and methods of biologic assay and measurement; on clinical research in the University College Hospital; on external research schemes; on industrial health, and on traveling fellowships. This report will be of interest and a stimulus to those who are engaged especially in any of the problems with which it deals, as well as to those who are concerned with medical research in general.

**La spirochétose méningée.** By Jean Troisier, Professeur agrégé à la Faculté de Médecine de Paris; Médecin de l'Hôpital Beaujon et Yves Boquien; Interne des Hôpitaux de Paris. Price, 34 francs. Pp. 187. Paris: Masson & Cie, 1933.

In this monograph is described in minute detail a leptomeningitic form of icterohemorrhagic spirochetosis or leptospirosis (Weil's disease, epidemic jaundice). The description is based on the reports of twenty cases observed by French clinicians. The authors make it clear that forms of acute meningitis may be caused by *Spirochaeta* or *Leptospira icterohaemorrhagiae*. No deaths occurred in the series of cases reported.

## Books Received

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**CALCIUM METABOLISM AND CALCIUM THERAPY.** By Abraham Cantarow, M.D., Instructor in Medicine, Jefferson Medical College; in charge of Laboratory of Biochemistry, Jefferson Hospital; Assistant Physician, Philadelphia General Hospital. With a Foreword by Hobart Amory Hare, B.Sc., M.D., LL.D., Late Professor of Therapeutics, *Materia Medica and Diagnosis* in the Jefferson Medical College, Philadelphia. Second edition. Price, \$2.50, net. Limp binding. Pp. 252. Philadelphia: Lea & Febiger, 1933.

**THIRD REPORT OF THE MINERS' NYSTAGMUS COMMITTEE.** Medical Research Council, Special Report Series, No. 176. Price, 9 pence, net. Pp. 36. London: His Majesty's Stationery Office, 1932.

**ETUDE CLINIQUE DE L'ÉQUILIBRE ACIDE-BASE PAR L'ANALYSE D'URINE.** Par R. Goiffon. Price, 16 francs. Pp. 102. Paris: Masson et Cie, 1933.

**APPARATUS FOR THE RAPID STUDY OF ULTRA-VIOLET ABSORPTION SPECTRA.** By J. St. L. Philpot and E. H. J. Schuster, Medical Research Council, Special Report Series, No. 177. Price, 1 shilling, 3 pence, net. Pp. 45. London: His Majesty's Stationery Office, 1933.

**NEUROPATHOLOGY: THE ANATOMICAL FOUNDATION OF NERVOUS DISEASES.** By Walter Freeman, M.D., Ph.D., D.N.B., F.A.C.P., Professor of Neurology, George Washington University; Director of Laboratories, St. Elizabeth's Hospital, Washington, D. C. Price, \$4. Pp. 349, with 116 illustrations. Philadelphia: W. B. Saunders Company, 1933.

**REPORT OF THE MEDICAL RESEARCH COUNCIL FOR THE YEAR 1931-1932.** By the Committee of the Privy Council for Medical Research. Presented by the Lord President of the Council to Parliament by Command of His Majesty, February, 1933. Price, 2 shillings, net. Pp. 140. London: His Majesty's Stationery Office, 1933.

**CHRONIC ENTERIC CARRIERS AND THEIR TREATMENT.** By C. H. Browning with H. L. Coulthard, R. Cruickshank, K. J. Guthrie and R. P. Smith. Medical Research Council, Special Report Series, No. 179. Price, 1 shilling, 6 pence, net. Pp. 80. London: His Majesty's Stationery Office, 1933.

THE ARCHIVES OF PATHOLOGY is published by the American Medical Association as a medium to advance the science of pathology in the United States and for the promotion of research and observation in this field.

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